14th Annual Postdoc Scientific Symposium

March 22, 2018
11:00 am – 5:00 pm
Eric P. Newman Education Center

Sponsored by
The Office of the Vice Chancellor for Research
The Office of Postdoctoral Affairs
The Washington University Postdoctoral Society

Washington University in St. Louis
Schedule of Events

11:00am  Welcome and Panel Discussion
          EPNEC Auditorium
          Jennifer K. Lodge, Ph.D.
          Vice Chancellor for Research
          Professor, Department of Molecular Microbiology

          The Stories Behind a C.V.
          Moderators: Carissa Dege, Ph.D. and Francisco Victorino, Ph.D.
          Greg Bowman, Ph.D.
          Assistant Professor, Department of Biochemistry and Molecular
          Biophysics, Washington University
          Nikkilina Crouse, Ph.D.
          Senior Medical Science Liaison, Teva Neurosciences
          Lydia-Ann Harris, Ph.D.
          Instructor in Medicine, John T. Milliken Department of Medicine,
          Washington University School of Medicine
          Thi Nguyen, Ph.D.
          Associate Dean for Graduate Career and Professional Development,
          The Graduate School, Washington University

12:30pm  Postdoctoral Research Talks

          Role of microglia during West Nile virus encephalitis
          Kristen Funk, Ph.D.
          Faculty Mentor: Robyn Klein, M.D., Ph.D.
          John T. Milliken Department of Medicine, Division of Infectious
          Disease, Washington University School of Medicine

          89Zr-M9346A immuno-PET imaging folate receptor alpha
          in triple negative breast cancer for image-guided
          intervention with mirvetuximab soravtansine
          Gyu Seong Heo, Ph.D.
          Faculty Mentor: Yongjian Liu, Ph.D.
          Mallinckrodt Institute of Radiology, Washington University School of
          Medicine
Schedule of Events

An exploration of the biological response to remote limb ischemic conditioning in humans
Anna Mattlage, Ph.D.
Faculty Mentor: Catherine Lang, P.T., Ph.D.
Program in Physical Therapy, Washington University School of Medicine

Development of a virtual reality paradigm for in vivo hippocampal imaging during morphine conditioned place preference
Sidney Williams, Ph.D.
Faculty Mentor: Jose Moron-Concepcion, Ph.D.
Washington University Pain Center

Electron cryo-microscopy structure of Ebola nucleoprotein reveals a mechanism for nucleocapsid-like assembly
Chao Wu, Ph.D.
Faculty Mentor: Gaya Amarasinghe, Ph.D.
Pathology and Immunology, Washington University School of Medicine

2:15pm
Keynote Address
EPNEC Auditorium
My Life as a Scientist, Administrator, and Woman
Elizabeth L. Travis, Ph.D.
Assoc. VP for Women and Minority Faculty Inclusion; Professor in Cancer Research; University of Texas, M.D. Anderson Cancer Center

Presentation of the Outstanding Faculty Mentor Award

3:30pm-5:00pm
Poster Session and Resource Fair
EPNEC Great Rooms

Resource Fair Participants: Pages 11-16
Poster Abstracts: Pages 18-51
Even numbered posters manned from 3:45-4:15pm
Odd numbered posters manned from 4:15-4:45pm
Evaluations will be sent via email we appreciate your feedback.
Keynote Speaker:
Elizabeth L. Travis, Ph.D.

Dr. Travis is the Associate Vice President for Women & Minority Faculty Inclusion Programs and the Mattie Allen Fair Professor in Cancer Research at The University of Texas MD Anderson Cancer Center in Houston, Texas. As an advocate for women in science, she served as President of Women Executives in Science and Healthcare (Formerly Society of Executive Leadership in Academic Medicine, SELAM) from 2012-2013 and received the Women in Medicine and Science Leadership Development Award (for an individual) from the Association of American Medical Colleges (AAMC) in 2009. In 2007 she was named a Fellow of the American Society for Therapeutic Radiation Oncology (FASTRO); fewer than 300 distinguished scientists nationwide have received this honor. She holds dual appointments as a Professor in the Department of Experimental Radiation Oncology and the Department of Pulmonary Medicine at MD Anderson. Dr. Travis received a Ph.D. in Experimental Pathology/Radiation Biology from the Medical University of South Carolina in Charleston, South Carolina. She completed postdoctoral training at Mount Vernon Hospital Gray Laboratory, Northwood, Middlesex as well as the Kellogg School of Management at Northwestern University in Chicago, Illinois.
Panelists

Stories Behind a CV
A person’s CV tells the official, polished trajectory of their career path, but what is the real story behind the CV? As scientists, we face many struggles such as failed experiments, doubts about our abilities and indecision about which career path is best for us. Looking at our peers and mentors it can feel like everyone else has it all figured it, but do they? The path to a successful career is not always perfect, in fact it usually happens in fits and starts with a few curveballs thrown in. Today our panel will pull back the curtain and tell us their ‘unofficial’ CV. They will discuss the obstacles they faced and how they overcame them, as well as personal and professional factors that influenced their career decisions.

Greg Bowman, Ph.D.
Assistant Professor, Department of Biochemistry & Molecular Biophysics, Washington University
Dr. Bowman’s lab combines computer simulations and experiments to understand protein dynamics, how they are connected to a protein’s function, and new opportunities this insight opens up for designing new drugs and proteins. He earned his Ph.D. from Stanford University, where he developed new computational methods for simulating long timescale events, such as protein folding. Then won a Miller Research Fellowship at UC Berkeley, where he began combining simulations and experiments to understand allosteric communication between distant regions of a protein. He then won a Burroughs Wellcome Fund Career Award at the Scientific Interface, which helped enable his transition to WUSM in 2014. The Bowman lab has grown to 9 members and secured a number of grants, including an NSF CAREER Award, a Packard Fellowship in Science & Engineering, and multiple NIH grants.

Nikkilina Crouse, Ph.D.
Senior Medical Science Liaison (MSL), Teva Neurosciences
Dr. Crouse is currently a Senior MSL on the Movement Disorders and Psychiatry team at Teva. Her job focuses on being a scientific, educational resource internally and externally on the topics of Huntington’s Disease and Tardive Dyskinesia. In the field, she spends time helping physicians understand the disease states, sharing clinical data, assisting with clinical trials and providing updates from conferences. Internally, she serves as a reviewer for scientific communications and pharmaco-vigilance, a training liaison for the commercial organization and a mentor to other MSLs. Prior to joining Teva, she earned her PhD in Biochemistry from the University of Missouri-St. Louis where her research focused on immune responses in Alzheimer’s Disease. Following graduation, she accepted a contract position at Pfizer in Chesterfield performing pre-clinical research in Multiple Sclerosis. At the end of the contract, she joined the lab of David H. Gutmann, M.D., Ph.D. at Washington University School of Medicine as a Postdoctoral Fellow in the field of neurofibromatosis. She joined Teva in 2012 as a Parkinson’s Disease M.S.L.
Lydia-Ann Harris, Ph.D.
Instructor in Medicine, John T. Milliken Department of Medicine, Washington University School of Medicine

Dr. Harris is a non-tenure track Research Instructor at the Center for Human Nutrition. Dr. Harris came to the U.S. from the island of Saint Lucia to study biology at St. Francis College, Brooklyn N.Y. where she earned her Bachelor’s degree. She completed her Ph.D. in Biological Sciences in Dr. Gerald Koudelka’s lab at SUNY-Buffalo. In the Koudelka lab, she studied the mechanism of DNA sequence recognition by the P22 bacteriophage repressor protein. She then completed her postdoctoral research fellowship at the Center for Human Nutrition at Washington University School of Medicine. Her postdoctoral research focused on the roles of the lipid droplet-regulating protein, Perilipin 5 (PLIN5), and metabolic hormone, fibroblast growth factor (FGF) 21 in lipid storage and glucose metabolism in mice. As a postdoc she was also involved in several organizations such as the WashU Postdoctoral Society, the BALSA Group and the Young Scientist Program. Dr. Harris is currently pursuing a translational research program studying the significance of FGF19, FGF21 and bile acids to metabolic health in persons with obesity, diabetes and non-alcoholic fatty liver disease (NAFLD).

Thi Nguyen, Ph.D.
Associate Dean for Graduate Career and Professional Development, The Graduate School, Washington University

Dr. Nguyen leads the development and implementation of programs that promote career readiness. Thi has experience providing career advice for graduate students at a national level on platforms such as ScienceCareers, NatureJobs, and a Reddit Ask Me Anything. Her expertise on careers beyond the tenure track comes from working with employers and consultants in the Bay Area, Boston, and now St. Louis. She has navigated advisors moving during her doctoral and postdoctoral training, and a recent dual career search, and enjoys advising on how to best position yourself to land a job. After her postdoc at the Gladstone Institutes, she has worked as program director at a career center, consultant, visiting scientist with an academic research group, freelance grant evaluator, primary investigator of foundation grants, and SBIR ghost writer. Thi has a PhD in Neuroscience from UT Southwestern Medical Center.
Role of microglia during West Nile virus encephalitis

Kristen Funk

Funk KE, Boker M, Klein RS

Internal Medicine-Infectious Diseases
Faculty Mentor: Robyn Klein

Microglia are the native immune cells of the central nervous system (CNS), however, their role during viral infection of the CNS is not entirely clear. We hypothesize that microglia help control the initial viral infection, then act as the antigen presenting cells in the CNS, necessary to recruit and locally re-stimulate T lymphocytes, which clear the virus. To test this hypothesis, we used PLX5622, an antagonist to colony stimulating factor 1 receptor (CSF1R), provided in standard mouse chow. After two weeks of PLX5622 treatment, microglia are depleted by about 90%. Mice depleted of microglia succumb to peripheral infection of the virulent strain of WNV (NY99) significantly more than mice fed control chow. This is accompanied by increased viral burden within the CNS; however, there is also significant loss of virologic control in peripheral organs. In order to determine whether CNS infection is sufficient to cause the survival phenotype, mice were infected with an attenuated strain of WNV (NS5-E218A) via intracranial inoculation. Attenuation of this virus allows for more efficient targeting by innate immune mechanisms that limit peripheral organ infection. Depletion of microglia prior to intracranial infection with WNV-NS5-E218A increases mortality from 20% to 70%. To determine whether this may be due to deficient recruitment and activation of T lymphocytes within the CNS, flow cytometry was performed on CNS immune cells following intracranial infection of WNV-NS5-E218A. Results show that microglial depletion does not impact recruitment of adaptive immune cells, but data suggest that these cells may lack full activation. Together, these data suggest that microglia are critical in protecting the CNS from fatal viral encephalitis.
Mirvetuximab soravtansine (IMGN853), an antibody drug conjugate currently undergoing clinical trials in triple negative breast cancer (TNBC), ovarian cancer, and endometrial cancer patients, comprises the humanized folate receptor α (FRα)-binding M9346A antibody linked to the tubulin-disrupting maytansinoid, DM4. The clinical approach for patient screening is immunohistochemical assessment of archival tumor or biopsy samples, which may suffer from limitations of tumor heterogeneity and limited tissue collection. Herein, we developed zirconium-89 (89Zr) radiolabeled M9346A antibody as a PET imaging tool to assess the expression of FRα in whole TNBC tumors and guide the treatment using IMGN853. The binding specificity and immunoreactivity of 89Zr-M9346A were determined by in vitro studies in FRα high HeLa cells and FRα low OVCAR-3 cells. PET imaging in HeLa xenografts showed high tracer accumulation in tumor and the in vivo targeting specificity was confirmed by the competitive blocking studies. PET imaging in TNBC patient derived xenografts (PDXs) with various levels of FRα expression demonstrated specific and sensitive detection of FRα in tumors, which was confirmed by RT-PCR and immunohistochemistry. Treatment studies were performed in a FRα high and a FRα low PDX models, and their efficacy was evaluated by measurement of tumor volume and PET imaging during treatment. In contrast to the chemotherapy drugs showing little therapeutic effect in both PDX models, IMGN853 showed effective inhibition of tumor growth in the FRα high PDX model but not in the FRα low PDX model. The uptake of 89Zr-M9346A in FRα high tumors was significantly decreased following IMGN853 monotherapy targeted treatment, which was consistent with tumor mass variations during the treatment.
An exploration of the biological response to remote limb ischemic conditioning in humans

Anna Mattlage

Gidday J, Stein P, Lee JM, Hershey T, Chen L, Lang CE

Program in Physical Therapy
Faculty Mentor: Catherine Lang

Remote limb ischemic conditioning (RLIC) is a technique in which tissues are exposed to brief, sub-lethal bouts of ischemia. The effects are transferred via blood to the target organ, usually for protection from subsequent ischemic injury. The autonomic nervous system (ANS) is thought to trigger the beneficial blood factors. Specific blood markers of RLIC have not yet been identified. This information, however, would increase our understanding of the mechanism of RLIC and allow us to identify when RLIC has been successfully administered. The current work is an ongoing exploration of RLIC biological response. Healthy participants age 18-40 years were randomized to receive either RLIC (n=6) or sham conditioning (n=6) (five, 5-minute cycles of inflation/deflation of a blood pressure cuff on the upper extremity) once a day for 7 consecutive weekdays. Inflation for RLIC and sham conditioning was set at 20 mmHg above systolic blood pressure (BP) and 10 mmHg below diastolic BP, respectively. Heart rate variability (HRV, ANS response to conditioning) was calculated from 5 minute EKG recordings taken before, during and after conditioning on Day 1. Blood was sampled on Days 1, 2 and 7 before conditioning and on Day 1 after conditioning. A SOMAscan assay quantified 1,317 analytes in the blood and the top candidates were identified. An exploration of HRV suggests that individuals receiving sham conditioning have no HRV response, while individuals in the RLIC group have a HRV response. Several analytes in the blood had a significant response to RLIC compared to sham. This study provides preliminary evidence of the biological response to RLIC in healthy adults. Continued work is needed to determine if HRV/blood markers can be used to confirm successful administration of RLIC.
Development of a virtual reality paradigm for in vivo hippocampal imaging during morphine conditioned place preference

Sidney Williams

Williams SB, Arriaga MW, Post W, Han EB, Moron JA

Anesthesiology
Faculty Mentor: Jose Moron-Concepcion

Opioids, like other drugs of abuse, result in structural and functional changes in the hippocampus, leading to long-lasting associations between the opioid-induced reward and the environment; possibly mediating relapse of drug-taking behavior. Using ex vivo approaches, our lab has shown that morphine conditioned place preference (mor CPP) decreases the number of dendritic spines of hippocampal CA1 neurons, mediated by NR2B containing NMDA receptors, yet the timing and dynamics of these events and their potential relationship to the association between drug reward and context are unknown. To observe neural networks in real time as mor CPP and reinstatement take place, we have designed a virtual reality conditioned place preference (VR-CPP) paradigm that can be paired with two-photon imaging. The three chamber VR-CPP apparatus contains a neutral middle chamber and two conditioning chambers containing distinct visual cues. Mice are head fixed in the VR environment and allowed to freely run on a Styrofoam ball suspended by air pressure. Movement of the ball is tracked, converted to forward and yaw velocities by custom written software in LabView, and then fed to a virtual reality engine written in Matlab, which updates the visual scene permitting the animal to navigate through the VR environment. Mice are trained to control their position in the VR by operant conditioning using H2O rewards, then are submitted to a biased mor CPP paradigm. After 8 days of mor-paired contextual conditioning, mice demonstrate a significant shift in place preference for the VR mor-paired. When combined with two-photon in vivo imaging, this novel behavioral paradigm allows unprecedented spatio-temporal resolution in following the structural and plasticity changes that underlie mor CPP.
Electron cryo-microscopy structure of Ebola nucleoprotein reveals a mechanism for nucleocapsid-like assembly

Chao Wu


Path & Immunology
Faculty Mentors: Gaya Amarasinghe and Daisy Leung

Ebola virus nucleoprotein (eNP) assembles into higher-ordered structures that form the viral nucleocapsid (NC) and serve as the scaffold for viral RNA synthesis. However, molecular insights into the NC assembly process are lacking. Using a hybrid approach, we characterized the NC-like assembly of eNP, identified novel regulatory elements, and described how these elements impact eNP functions. We generated a three-dimensional reconstruction of the eNP NC-like structure at 5.8Å using electron cryo-microscopy and identified a new regulatory role for eNP helices a21-a23. Biochemical, biophysical, and mutational analysis revealed inter-eNP contacts within a21-a23 that are critical for viral NC-assembly and regulate viral RNA synthesis, suggesting that a21-a23 and the N terminus of eNP function as context dependent regulatory modules (CDRMs). Our current study provides a framework for a structural mechanism for NC-like assembly and identifies new therapeutic targets.
Washington University Postdoctoral Society (WUPS)
The Washington University Postdoctoral Society (WUPS) was established by postdoctoral researchers in 2003. Our mission is to support postdocs by providing events to foster career development and a sense of community. As a postdoc researcher at WashU, you are automatically a member of the postdoc society and have unlimited access to all events and seminars associated with WUPS. WUPS recognizes that the postdoctoral appointment requires auxiliary and advanced training so that you may have access to a diverse range of career opportunities. In concert with the Office of Postdoctoral Affairs (OPA), WUPS facilitates and addresses postdoc concerns and needs with WashU administrators and faculty. We invite you to join our monthly meetings every first Thursday of the month. Being an active participant of WUPS provides you with the opportunity to meet administrators and faculty, and attend seminars/events that are critical for career advancement and your training experience here at WashU.

Seminars and Events we host:
- Academic Career Development
- Writing Workshops
- Immigration and Naturalization
- Alternative Careers in Science
- Cultural Events
- Community Events
- Happy Hours
- Networking with Faculty Members

WashU web address: postdoc.wustl.edu/postdocs/resources
WUPS email: postdocsociety@wustl.edu

The Office of Postdoctoral Affairs (OPA)
The OPA supports and advocates for all postdoctoral research associates and scholars at Washington University. The office provides career and professional development training and is a central resource for information regarding postdoctoral training. We assist in the development and support of a diverse community of postdoctoral researchers.

Website: postdoc.wustl.edu (updated March 2018)
Email: postdoc@email.wustl.edu
BALSA
The Biotechnology and Life Sciences Advising Group (BALSA) was founded in 2010 by a group of biomedical Ph.D. candidates and postdoctoral fellows from the WashU School of Medicine. Its goal is to supplement academic training by providing real-world experience in the science of business and development of transferable professional skills to better prepare members for academic and non-academic career paths. BALSA further aims to offer a bridge between academia and industry, fostering collaborations between local universities and companies, to strengthen the young but vibrant St. Louis startup community. BALSA has grown to encompass over 100 active members from WashU, St. Louis University (SLU), and the St. Louis professional community. Consultants come from a myriad of backgrounds including cell biology, neuroscience, immunology, microbiology, genetics and genomics, cancer biology, plant biology, chemistry, engineering, business and law. While members enter with little experience in professional consulting, BALSA harnesses the analytical power of graduate students and postdocs by teaching them to apply the scientific method to business problems to generate innovative, data-driven solutions for clients. Consultants learn the market research skills necessary to deliver these recommendations through teamwork and peer-to-peer mentoring with experienced project managers and advisors.
Website: thebalsagroup.org

Clinical Research Training Center (CRTC) TL1 Translational Sciences Postdoctoral Program (TSPP)
The CRTC TL1 TSPP provides career development for postdoctoral trainees in medicine and allied health fields through active participation in mentored clinical and translational research, journal clubs, coursework, work-in-progress research discussions, and conferences. The objective of the TL1 TSPP is to demystify the processes of commercialization of translating research findings, including studying the methods to disseminate and implement new findings. The scope of the TL1 program is translational science from bench-to-bedside and bedside-to-bench research. The program has the broad ability to include research projects in late stage preclinical, first-in-human, clinical, translational, patient-oriented research, population health and community engagement, and biomedical informatics.
Program Dir: Jay F. Piccirillo, MD, FACS; Program Manager: Adisa Kalkan, MA
Website: crtc.wustl.edu
English Language Programs (ELP)
The English Language Programs (ELP) provides English language support designed to refine the English communication skills of nonnative English speakers in the university community, and to facilitate their academic and professional success at Washington University in St. Louis and beyond. This English communication support includes courses, tutorials, appointment-based individual help, and opportunities for informal English conversation practice. Of these services, only courses and tutorials require tuition. This tuition charge can be waived for postdoctoral appointees who are eligible for the university’s Postdoctoral Appointee Tuition Benefit.
Website: oiss.wustl.edu/english-language-programs
Email: elp@wustl.edu

Future Educators
Future Educators is a student-run group of graduate students and postdocs at Washington University in St. Louis who are passionate about teaching and mentorship in the STEM disciplines. We facilitate networking opportunities and meet regularly to discuss education research as well as teaching and mentorship opportunities. Our vision is to create a community that fosters development of the next generation of STEM educators and mentors. We strive to bring together trainees at Washington University who are passionate about teaching and mentorship and help them achieve their goals in education. Involvement in the group can range from periodic attendance at group events to leadership opportunities.
Website: futureeducatorswus.wixsite.com/about
Email: futureeducators.wustl@gmail.com to join our mailing list!

InPrint - A scientific editing network
InPrint is a trainee-run scientific editing network that provides free, confidential editing of scientific communication to the Washington University research community. If you are working on a manuscript or grant and would like constructive feedback to make it more polished, consider submitting your work to us today! We offer free editing of a broad range of communication types (abstracts, manuscripts, grants, posters, dissertations, graphical work, etc.) and also will design scientific schema upon request. Our mission is to improve the quality of
Resource Fair

scientific communication, encourage discussions among authors during the writing process, and enhance student and postdoctoral communication skills. We also aim to support trainee professional development with opportunities in science writing or editing by sponsoring communication-related workshops and events. Visit our website to submit your work and learn about how you can join the editing team!
Website: inprintscience.wustl.edu

The Office of the Ombuds
The Office of the Ombuds provides confidential, impartial, informal, and independent conflict resolution and problem-solving assistance to all university staff, postdoctoral appointees, Graduate School students and faculty. The Ombuds offers a safe place for individuals to voice university-related concerns and review options to manage those concerns. Additionally, the Ombuds serves as a catalyst for change by identifying patterns or trends on campus, offering feedback, and making recommendations about university policy or practice to those who may have the power to affect change. People visit an Ombuds for many reasons. Some just want someone to listen. Some want someone to serve as an objective sounding board that can help them think through a situation. Some want information about how a university policy or practice applies to them. Some are uncertain about how to navigate a difficult situation. And some have tried other avenues to address their concern but haven’t found the help they needed. Whether as a first step, a last resort, or somewhere in between, the Office of the Ombuds is here to help. No problem is too big or too small. The Ombuds is available to meet on both the Danforth and Medical campuses.
Website: ombuds.wustl.edu

Sling Health
Sling Health is a student-run, non-profit organization that supports students in the development and commercialization of med-tech solutions. Through our experimental platform, student-led teams embark on a nine-month program, which includes clinical assessment, prototype creation, and business development. We provide teams with the necessary resources, support, and mentorship to bring their ideas to life and solve real clinical problems submitted by clinicians and physicians.

*Come to our Demo day! April 13, 6 - 9 PM, @ 4240 Duncan Ave, St. Louis*
Website: slinghealth.org
The Teaching Center
The Teaching Center provides teaching-related support to WUSTL postdocs through a variety of services. We offer disciplinary teaching workshops that are structured around evidence-based pedagogical scholarship. These workshops examine strategies for effective teaching, spark new ideas, and deliver additional resources for teaching in your field. We also host a number of teaching-with-technology training opportunities, as well as job market workshops, which highlight different aspects of job market materials related to teaching including the teaching philosophy statement, the teaching portfolio, and the teaching demo. The Teaching Center staff also conducts confidential teaching observations and feedback on your teaching, which can strengthen your teaching now and help you prepare for a career in academia. In addition, we give individual consultations for a wide variety of teaching concerns like troubleshooting a classroom issue, motivating student learners, and developing active learning strategies. Postdocs may choose to participate in our professional development programs, Preparation in Pedagogy and WU-CIRTL (for postdocs in STEM fields). These programs are excellent teaching-related training opportunities, which also make nice additions to your CV. Finally, we have a number of web resources on teaching and teaching with technology.
Website: teachingcenter.wustl.edu

The Office of the Vice Chancellor for Research (OVCOR)
Responsible Conduct of Research
Researchers have important professional and regulatory responsibilities related to the responsible conduct of research (RCR), which is broadly defined as the practice of scholarship and scientific investigation with integrity.

- NIH guidelines for RCR state all undergraduates, graduate students, and postdocs on NIH training grants, career awards, or fellowships are required to receive 8 hours of RCR education.
- NSF guidelines for RCR state all undergraduate, graduate students, and postdocs on any NSF award are required to receive 1 hour of face-to-face education per year, in addition to one-time completion of the online PERCSS curriculum.
Program for the Ethical and Responsible Conduct of Science and Scholarship (PERCSS)

The PERCSS Core Curriculum features eight web-based (Learn@Work) learning modules related to ethics: Introduction to Ethical and Responsible Research; Authorship & Publication; Collaborative Research; Conflict of Interest; Data Ownership, Acquisition, Sharing, & Management; Mentor-Trainee Relationships; Peer Review; Research Integrity. The annual PERCSS Workshop features presentations and faculty-led case study discussions on WashU policies and procedures related to RCR. Anyone engaged in research and interested in RCR at WashU is welcome to attend. It is highly recommended for postdocs, career award recipients, and other junior research team members.

*The PERCSS Workshop is on April 6, pre-register through Learn@Work.*

Funding Resources

The OVCR offers a variety of resources to help identify and pursue federal and private sources of funding. A competitive funding environment often requires researchers to be creative in their search for support for their projects. A number of sources that identify and manage new funding opportunities are available to aid researchers. How to Find Funding: research.wustl.edu/funding

SPIN provides intuitive and easily customizable access to the most extensive research funding opportunity database. Create customized search notifications in SPIN and learn more at spin.wustl.edu.


The Research News listserv is designed to disseminate important research-related information and funding opportunities. Manage your subscription at: researchnews.wustl.edu.

The OVCR coordinates the Internal Selections Process, competitions in which funders restrict the number of applications per institution. Information about this process (used to select the University’s nominees) is available at: research.wustl.edu/funding/internal-selections.

To distribution list for Internal Selection announcements contact Catherine Determan, Funding Resources Coordinator, cdeterman@wustl.edu and 314.747.1654.
Poster

Abstracts
Semisynthetic Analogues of Anhydrotetracycline as Inhibitors of Tetracycline Destructase Enzymes

Jana Markley

Markley JL, Fang L, Symister CT, Gasparrini AJ, Dantas G, Tolia NH, Wencewicz TA

Chemistry
Faculty Mentor: Timothy Wencewicz

The preemptive understanding of the factors that affect newly emerging antibiotic resistance mechanisms is central to the development of efficient treatments of infectious diseases. In particular, those resistance mechanisms that proceed via enzymatic inactivation of “essential medicines” - through substrate modification and degradation pathways - pose a dangerous threat to the global population. While the clinical presentation of resistance via enzymatic degradation is prevalent and well established for β-lactam, amphenicol, and aminoglycoside antibiotics, the appearance of such resistance pathways for the tetracyclines, a widely used family of polyketide natural product and natural product-derived broad-spectrum antibiotics, was only recently observed in a clinically relevant setting. However, though ribosomal protection and substrate efflux are the main mechanisms of tetracycline resistance observed in human infection, enzymatic inactivation is the most important mechanism to elucidate and combat, as pathways that improve antibiotic clearance often dominate resistance landscapes. In this regard, we herein report the synthesis and biological evaluation of a small panel of anhydrotetracycline (aTc) analogues as potential inhibitors of tetracycline-inactivating enzymes. Studies focus on: (1) the formation of semisynthetic aTc analogues via acid-catalyzed dehydration or electrophilic aromatic substitution; (2) the in vitro evaluation of each aTc analogue as inhibitors of 3 representative tetracycline-inactivating enzymes against a sampling of potential tetracycline substrates; (3) the ability of the aTc panel to rescue tetracycline activity in corresponding whole cell assays.
High Pressure Investigations on the Semi-Heusler Compound CuMnSb

Pallavi Malavi

Malavi PS, Song J, Bi W, Regnat A, Bauer A, Senyshyn A, Pfleiderer C, Schilling JS

Physics
Faculty Mentor: James Schilling

CuMnSb is antiferromagnetic with a Néel temperature near 50K. We investigated this compound under pressure by using a diamond-anvil-cell. Four-point electrical resistivity measurements up to 500,000 atmospheres (50 GPa) and synchrotron x-ray diffraction to 30 GPa were carried out. Up to 7 GPa, pressure is found to enhance the Néel temperature. Above this pressure the temperature dependence of the resistivity shows a dramatic change associated with a first-order structural transition from cubic to a lower symmetry structure. The diffraction peaks of the high pressure phase are significantly broadened, suggesting its metastable nature. In a second x-ray experiment the diamond-anvil-cell was heated resistively to 350°C to complete the phase transition. Our study highlights the importance of pressure as a tool to explore novel electronic and structural phases in this interesting magnetic material.
How does flagellar beating change during regrowth in Chlamydomonas reinhardtii?

Mathieu Bottier

Bottier M, Dutcher SK, Bayly PV

Mechanical Engineering and Materials Science
Faculty Mentors: Philip Bayly and Susan Dutcher

Cilia and flagella are highly conserved organelles that generate propulsive, oscillatory waveforms that propel cells or move fluids. The mechanism of oscillation is a mystery. To distinguish competing models we studied the effects of regrowth on frequency and waveform in the unicellular alga Chlamydomonas reinhardtii using high-speed video-microscopy with bright field optics. Wild-type uniflagellate mutant Chlamydomonas cells were deflagellated by pH shock. During regrowth, using methods developed in our labs, we obtained high-resolution, mathematical descriptions of the waveform at different lengths. We recorded 97 videos of beating flagella that varied from 0.7 to 10.9 µm. Videos were recorded at 2000 frames/s with 169x169 nm spatial resolution. We discovered that the beat frequency is reduced for flagella less than 4 µm but stabilizes near 60 Hz (60.2 ± 20.7 Hz) when flagella are longer than 4 µm. The average curvature is small and variable in flagella less than 4 µm, and reaches a plateau at -0.20 ± 0.08 rad/µm for flagella less than 4 µm. Other quantities such as beat amplitude, mean bend amplitude, torque, power, and average force applied by the flagellum to the fluid in both the x and y directions, all increase with flagellar length. These results indicate that frequency and curvature are important conserved features of the flagellar waveform during regrowth. Because the average curvature is consistent, the total bend angle increases with flagellar length; i.e., waveforms of small flagella are not scaled versions of the waveform of longer flagella. These results suggest that the local mechanics of the axoneme are stable in flagella less than 4 µm and that changes in flagella length alone can explain qualitative changes in the waveform shape.
Robust Acoustic Focusing in Microfluidic Channels Using a Novel Piezoelectric Transducer Topology

Husain Shekhan

Shekhan HN, Meacham JM

Mechanical Engineering & Materials Science
Faculty Mentor: Mark Meacham

Hydrodynamic forces are used to manipulate cells in conventional flow cytometry; however, this mechanism provides weak confinement as throughput is increased. As an alternative, acoustic focusing driven by piezoelectric actuation offers researchers several unique opportunities, including rapid processing of dilute samples and exquisite control over the speed of cells as they pass through the instrument. Although these advantages are compelling, the acoustic phenomena that give rise to cell focusing are highly sensitive to factors that are difficult to control during industrial production of microfluidic channels (e.g., dimensional tolerances and microscopic properties of bonded surfaces). Further, device characteristics can change over the lifetime of the equipment. Significant parameter drift prevents operation at design conditions, degrading performance such that little or no acoustic focusing occurs.

To increase device robustness to potential variations in acoustic focusing behavior, a new piezoelectric transducer topology has been developed. By integrating two piezoelectric transducers in an opposing polarity format, a single actuator purposefully drives antisymmetric acoustic focusing for a wide range of structural and electrical conditions. Finite element modeling accounts for elastic (solid) and acoustic (fluid) behavior to allow identification and explanation of device attributes. Glass and silicon microchannels are fabricated, assembled and evaluated for focusing performance. The device exhibits successful operation over a large frequency bandwidth, proving its robustness versus traditional piezoelectric transducer-driven acoustic focusing.
Characterization of Lagging Strand DNA Polymerase Delta

Tanumoy Mondol

Mondol T, Stodola JL, Soranno A, Galletto R, Burgers PM

Biochemistry and Molecular Biophysics
Faculty Mentor: Peter Burgers

DNA polymerase delta (Pol δ) is responsible for elongation and maturation of okazaki fragments in the process of DNA replication from yeast to humans. In S. Cerevisiae, Pol δ is a three-subunit complex consisting of Pol 3 (125 kDa), Pol 31 (55 kDa), and Pol 32 (40 kDa), present at a 1:1:1 stoichiometry. We measured the rate of incorporation of a single nucleotide by a preformed DNA-Pol δ complex. The observed rate constant is 50 s⁻¹ which is higher than that observed previously. Proliferating cell nuclear antigen is a homotrimeric donut-shaped assembly that encircles DNA and is essential for processive DNA synthesis by Pol δ. When PCNA was loaded onto DNA, we observed that the PCNA-Pol δ complex incorporates a single nucleotide at a rate of > 350 s⁻¹. The importance of the interdomain connector loop and subunit-subunit interface of yeast PCNA for interaction with Pol δ has previously been investigated by introducing mutations. Although these mutations in PCNA severely affect the processivity of Pol δ during replication, it did not affect the PCNA triggered Pol δ catalytic rate significantly. The DNA binding properties Pol δ with a template-primer DNA labelled with fluorescein, have been investigated through the change in fluorescence intensity and fluorescence anisotropy, using fluorescence spectroscopy and confocal fluorescence microscopy. Steady state fluorescence intensity and fluorescence anisotropy binding studies indicate that Pol δ binding to template-primer DNA is significantly reduced when the salt concentration increases. Moreover, based on Electrophoretic Mobility Shift Assay, fluorescence Intensity changes and fluorescence anisotropy binding titration, we demonstrate that Pol δ forms higher order oligomers upon binding to DNA.
Structure and function of heme transporters in cytochrome c biogenesis

Molly Sutherland

Sutherland MC, Jarodsky JM, Kranz RG

Biology
Faculty Mentor: Robert Kranz

Heme is a critical co-factor for cellular function (e.g. oxygen transport and energy production). However, the cytotoxic nature of heme results in tight regulation of heme levels and trafficking, making direct investigation of heme trafficking and heme transporters difficult. Previously, we described a novel method called cysteine/heme crosslinking to trap heme as it is trafficked through the System I prokaryotic cytochrome c biogenesis pathway. Here, we apply this method to the System II cytochrome c biogenesis pathway. System II is composed of a ten transmembrane integral membrane protein called CcsBA which is proposed to transport heme and attach it to a conserved CXXCH motif on apocytochrome c. Using genetic, biochemical and heme trapping assays we have identified two heme binding domains in CcsBA, designated as the internal and external heme binding domains. These results suggest a molecular mechanism for heme transport by CcsBA whereby heme moves from the internal domain to the external domain, where it is stereochemical positioned for attachment to apocytochrome c. Interestingly, the external heme binding domains of System II (CcsBA) and System I (CcmC) have homologous residues involved with heme binding, allowing for speculation on the evolution of these pathways. We also can now structurally model this conserved external heme binding domain.
A non-canonical VSD-pore coupling is responsible for the AO state of KCNQ1 channel

Panpan Hou
Panpan H, Jingyi Shi, Cui J

Biomedical Engineering
Faculty Mentor: Jianmin Cui

In the heart, the voltage gated KCNQ1 potassium channel (Kv7.1) is critical for controlling the heart rhythm. Our recent studies found that, different from any other ion channels, KCNQ1 has a unique two open states gating mechanism. The channel is open when the voltage sensor domain (VSD) is activated to either the intermediate state (termed IO) or the fully activated state (AO). However, what kind of VSD-pore coupling is responsible for the two open states remains unclear. Using voltage clamp fluorometry, here we find that the IO and AO states can be selectively altered by two Long QT syndrome mutations: F351A at the c-terminal of S6 can selectively suppress the IO state VSD-pore coupling to eliminate the IO state, and S338F in the middle of S6 can selectively suppress the AO state VSD-pore coupling to eliminate the AO state, indicating that different VSD-pore coupling mechanisms are responsible for the IO and AO states, respectively. Further, we determined two more residues in the middle of S6, F339 and L342, that work similar as S338F. Considering that the canonical VSD-pore coupling happens between the S4-S5 linker and cytoplasmic end of S6, these results indicate that the middle part of S6 is involved in a non-canonical VSD-pore coupling selectively for the AO state.
Biochemical and Structural Characterization of a Host Protein that Binds VP30

Dandan Liu

Liu D, Small G, Batra J, Basler C, Leung D, Amarasinghe G

Pathology and Immunology
Faculty Mentor: Gaya Amarasinghe

Ebola and Marburg viruses are negative sense RNA viruses that can cause high case fatality rates during outbreaks. Approximately 19 kb genome encodes for 7 open reading frames. During virus replication, 7-10 multifunctional proteins are expressed, but viral replication and pathogenesis also require numerous cellular proteins. While the need for host factors in virus replication and pathogenesis has been long appreciated, our understanding of key host-virus interactions during filoviral infection and replication remain incomplete. In order to address this limitation, our collaborators recently performed a proteomic analysis, which identified RBBP6, an E3 ubiquitin ligase, as a cellular interactor of Ebola VP30 (eVP30). eVP30 is a viral protein critical for transcription initiation. In this study, we generated a series of recombinant RBBP6 and eVP30 truncation constructs. We performed in vitro pull-down assays to validate the initial proteomic identification of the eVP30/RBBP6 protein-protein interaction and defined key regions within RBBP6 that are critical for eVP30 binding. Furthermore, using purified eVP30 protein, we generated crystals with a RBBP6 binding peptide, which diffracted up to 1.8 Å. The x-ray crystal structure provides a molecular model for RBBP6 interaction with eVP30. At the completion, we expect to define a key host-viral interface that modulates viral pathogenesis and define a novel target for potential development of antiviral therapeutics that target filoviruses.
CP1 opens Iks channels by substituting PIP2

Yongfeng Liu


Biomedical Engineering
Faculty Mentor: Jianmin Cui

KCNQ1 voltage-gated potassium channel assembles with its KCNE1 auxiliary subunit to form the slow delayed rectifier (IKs) channel, which plays an important role in repolarizing action potentials in cardiac myocytes. Loss-of-function mutations in the KCNQ1 or KCNE1 gene have been associated with long QT (LQT) syndrome and lead to an elevated risk of fatal cardiac arrhythmias. The activities of KCNQ1 and IKs channel are regulated by phosphatidylinositol 4,5-bisphosphate (PIP2), which serves as a cofactor and maintain the coupling between the voltage sensor and pore. Using the previously identified PIP2 binding sites in a homology structural model of KCNQ1 as the target, we perform an in-silico screening of chemical compounds in the Available Chemical Database (ACD, Molecular Design, Ltd.) and a subsequent experimental testing on the IKs channels expressed in Xenopus oocytes and identify CP1 as a novel IKs opener. CP1 can enhance IKs currents amplitude by two-fold and is highly selective against KCNQ channels. Consistent with targeting the PIP2 binding site, CP1 rescues the IKs current with the coexpression of CiVSP, which depletes PIP2 and inhibits the currents. The KCNQ1/IKs specific blocker, Chromanol 293B inhibits the enhanced current due to CP1 application, suggesting that CP1 substitutes for PIP2 in activating IKs channels. In preliminary experiments with Guinea-pig ventricular myocytes, CP1 caused similar changes in chromanol sensitive IKs while also shortening action potential duration. CP1 as an opener of the IKs channels may provide a novel therapy to treat congenital and acquired LQT syndromes.
The Leukocyte Chemoattractant, Chemerin, Upregulates PTEN via CMKLR1 in Human Tumors

Keith Rennier

Rennier KR, Pachynski RK

Internal Medicine
Faculty Mentor: Russell Pachynski

The balance between anti-tumor effector and suppressive immune cells in the tumor microenvironment (TME) is key in determining a patient’s response to cancer treatment. Recent studies show modulating phosphatase and tensin homolog (PTEN) activity can directly affect T-cell mediated immunotherapies. Specifically, loss of PTEN was shown to promote resistance to T-cell mediated immunotherapy. Although, rescued PTEN signaling functions to repress the expression of programmed cell death ligand 1 (PD-L1), a known inhibitor of the host immune response. These studies further support the growing evidence that the oncogenic pathway affects antitumor immunotherapy strategies.

Chemerin (RARRES2; retinoic acid receptor responder 2) is an endogenous leukocyte chemoattractant previously shown to recruit innate immune cells in mouse tumor models. RARRES2 is commonly downregulated across multiple tumor types compared to normal tissue via microarray studies. Methylome-wide analysis in various tumor samples have identified RARRES2 as being one of the most hypermethylated genes, potentially leading to decreased chemerin expression. Therefore, we hypothesized that re-introducing chemerin to the TME may lead to suppressed tumor progression and activity.

To test this, we exposed human cancer cells to exogenous chemerin. We found recombinant chemerin was able to significantly upregulate PTEN mRNA and protein expression and activity. Additionally, this increased PTEN expression correlates with a decrease in PD-L1 expression after chemerin incubation. The chemerin-driven increased PTEN activity is mitigated when CMKLR1, a key chemerin receptor, is knocked down via siRNA. Overall, this study shows chemerin’s ability to increase PTEN activity and to mitigate tumor cell migration via CMKLR1.
Concurrent HER or PI3K inhibition potentiates the anti-tumor effect of ERK inhibitor BVD-523 (ulixertinib) in preclinical pancreatic cancer models

Hongmei Jiang

Hongmei J, Mai Xu, Lin Li, Highkin M, Zhang D, Qiong Li, Wang-Gillam A

Internal Medicine
Faculty Mentor: Kian-Huat Lim

To date, effective treatments for inoperable pancreatic ductal adenocarcinoma (PDAC) remain elusive. Targeting KRAS, the gene that is mutated in > 95% of PDAC, is a heavily pursued strategy, but unsuccessful in the clinic. Therefore, targeting key effector cascades of KRAS oncoprotein, particularly the mitogenic RAF-MEK-ERK represents the next best strategy. However, RAF or MEK inhibitors have not shown promising clinical efficacy in PDAC. Several studies have shown that cancer cells treated with RAF or MEK inhibitors adopt multiple mechanisms to re-activate ERK signaling. Therefore, development of ERK-specific inhibitors carries the promise to effectively abrogate this pathway. BVD-523 (ulixertinib) is a first-in-class ERK-specific inhibitor that has demonstrated anti-tumor activity in clinical trials. In this study, we showed that BVD-523 effectively inhibits transformed growth of multiple PDAC lines and potentiates the cytotoxic effect of gemcitabine. Moreover, using reverse-phase protein array analysis, we identified potential mechanisms by which PDAC cells may adopt to tolerate ERK inhibition. On this basis, we proposed and tested two rational combinatorial approaches with BVD-523 that showed promising preclinical efficacy in vitro and in mouse xenografts. Overall, we provide the first evidence that PDAC cells may readily adapt to pharmacologic ERK inhibition, and provide combinatorial therapeutic strategies that could benefit patients.
MAPK13 Induction Co-locates with MUC5AC to Mucin Granules

Benjamin Gerovac

Gerovac BJ, Yantis J, Brody SL, Keeler SP, Holtzman MJ

Pulmonary
Faculty Mentor: Michael Holtzman

Excess mucus production and consequent airway obstruction is a major factor in the morbidity and mortality of acute and chronic respiratory diseases, including asthma and COPD. However, the precise basis for increased mucus formation and effective means to specifically and safely down-regulate mucus to physiological levels remain uncertain. Previously, we discovered that IL-13-induced mucus production in primary-culture human airway epithelial cells (hTECs) was associated with selective MAPK13 activation and was blocked with MAPK13 inhibition using siRNA specific for MAPK13 mRNA or small-molecules designed to target the MAPK13 ATP-binding site. In addition, we found increased levels of activated MAPK13 in lung tissue from patients with excess mucus due to COPD. Therefore, we further studied MAPK13 to define activation and localization in relation to mucus production in hTECs. hTECs were cultured for 0-21 d +/- IL-13 and levels of phospho-MAPK13 (pMAPK13) were measured with a phospho-MAPK antibody array and cellular level and location of MAPK13 and mucin MUC5AC were monitored by confocal microscopy. The data showed pMAPK13 levels were quickly increased (by 0.5 h) and were maximal at 2 d of IL-13 treatment compared to controls. MAPK13 immunostaining was detectable at near background levels at 0-21 d without IL-13 treatment but was markedly increased to intense cytoplasmic staining in a subset of cells at 7-21 d with IL-13 treatment. These MAPK13-positive cells were also selectively and intensely stained positive for MUC5AC. Further, the pattern of MAPK13 and MUC5AC immunostaining in the cytoplasm was identical, consistent with co-localization of these proteins to mucin granules.
Structural disconnection plays a key role in brain network dysfunction after stroke

Joseph Griffis

Griffis JC, Metcalf NV, Siegel JS, Corbetta M, Shulman GL

Neurology
Faculty Mentors: Gordon Shulman and Maurizio Corbetta

Strokes cause focal lesions that produce physiological dysfunction in distributed brain networks. Functional connectivity (FC), a measure of correlated brain activity, enables the quantification of network dysfunction using functional MRI. While FC-derived measures of network dysfunction predict acute deficits after stroke, it is unclear how they relate to the focal lesion. This represents a gap in the current understanding of stroke pathophysiology, and poses an obstacle to the development of treatments that restore normal network function.

To address this gap, we investigated the relationship between lesion properties and previously identified FC abnormalities in a sample of 110 acute stroke patients. In addition to mapping each patient’s lesion topology and measuring regional cortical damage, we used a population-level structural connectome to obtain a novel measure of structural disconnection.

Analyses using summary-level descriptions of each lesion property (i.e. lesion size, total cortical damage, and total structural disconnection) revealed that while each measure correlated with abnormal FC, only total structural disconnection uniquely predicted abnormal FC. Analyses incorporating more complex descriptions of each lesion property revealed that structural disconnection patterns were superior to lesion topologies or cortical damage patterns for predicting abnormal FC, and indicated an important role of interhemispheric disconnections. In summary, acute post-stroke network dysfunction is likely driven largely by structural disconnection. This highlights structural disconnection as an important, but often overlooked, dimension of focal brain lesions that may be critical for understanding their distributed effects on network physiology.
Effect of a Proximal Crush Injury on Pain-Related Behavior in a Rat Neuroma Model

Alexandra Halevi

Halevi AE, Wood I, Wang J, Schellhardt L, Wood MD, Moore AMM

Plastic Surgery
Faculty Mentor: Amy M. Moore

Background: Development of painful neuromas after nerve injury is poorly understood. Painful neuromas are frequently treated surgically, but there is no consensus regarding optimal approach. Our study evaluated the effect of a proximal nerve crush in a rat sciatic nerve injury model to prevent or treat pain.

Methods: The experiment consisted of 2 arms: 1) neuropathic pain prevention, and 2) neuropathic pain treatment. Male Lewis rats (n=8) had a sciatic transection to induce nerve injury and pain-related behavior. This was followed by an intervention at one of two different time points (2 and 6 weeks following injury), where the animals underwent either a sham surgery, proximal crush, or neuroma resection. Cold allodynia pain behavior was measured for 3 months.

Results: Prior to nerve injury, rats demonstrated zero cold allodynia flinch time, which increased over time following the nerve injury. Pain prevention: At 3 months after the 2 week crush intervention, the crush group had a total cold allodynia flinch time of 5.7 ± 7.7 (mean ± standard deviation, seconds), and the resection group 23.0 ± 5.0 (p < 0.01). Sham flinch time was 14.2 ± 8.6, which was not significantly different. Pain treatment: By 6 weeks following the initial nerve injury, cold allodynia plateaued to a maximum of 22.6 ± 6.8. Following intervention, flinch time in the proximal crush group was 12.5 ± 5.5, the resection group 15.4 ± 10.5, and the sham group 22.1 ± 10. These were not statistically different.

Conclusions: These data show that early intervention with a nerve crush after nerve injury is able to modulate pain-related behavior. However, a 6 week intervention was not effective. These findings suggest a potential benefit of utilizing a nerve crush technique early after injury.
Stem cell models of autosomal dominant Alzheimer's disease (ADAD)

Sidhartha Mahali

Mahali SK, Hsu S, Benitez BA, Martinez R, Sands MS, Goate AM, Karch CM

Psychiatry
Faculty Mentor: Celeste M. Karch

Alzheimer’s disease (AD) is characterized by neuronal loss accompanied by the accumulation of extracellular plaque deposits of β-amyloid (Aβ) and intracellular aggregates of hyperphosphorylated tau. Mutations in amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2) are sufficient to cause autosomal dominant AD (ADAD). Yet, our understanding of disease mechanisms is limited. We sought to develop a humanized model of AD to identify basic disease mechanisms as well as to develop drug targets. We have banked fibroblasts from APP, PSEN1 and PSEN2 mutation carriers and non-carrier controls enrolled in the Dominantly Inherited Alzheimer Network (DIAN). We reprogrammed a subset of these fibroblasts into human induced pluripotent stem cells (iPSC). iPSCs were differentiated into cortical neurons in 2D and 3D, which may recapitulate the neural architecture in the human brain. We found that ADAD neurons produce elevated extracellular Aβ42 compared with controls. Beyond γ-secretase activity, PSEN1 and PSEN2 also play important roles in regulating lysosomal homeostasis, which could impact protein accumulation. ADAD neurons exhibited aggregation and altered distribution of lysosomal structures. Lysosome activity was also altered in a subset of ADAD neurons. Together, these changes could result in impaired lysosomal degradation and accumulation of disease-relevant proteins. As such, we observed tau accumulation in lysosomal structures in ADAD neurons. All of these phenotypes were enhanced in 3D culture and further verified in human ADAD brains. Together, this system provides an exciting model to understand the earliest AD phenotypes and to develop novel therapeutic targets.
Transferrable factor provides resistance to norovirus infection in immunodeficiency

Harshad Ingle

Ingle H, Lee S, Locke M, Overdahl A, Baldridge M

Internal Medicine
Faculty Mentor: Megan Baldridge

Norovirus (NoV) gastroenteritis is a major health problem leading to > 90% of viral gastroenteritis and serious illness, yet little is known about the factors controlling NoV spread. Previously, we have shown that the persistence of murine norovirus (MNoV) is enhanced by the presence of commensal bacteria and this is dependent on the Ifnl2/3 receptor. However, the role of B and T lymphocytes in regulating persistent MNoV infection is not clear. In the present study, we used a combination of immunodeficient mice to determine the importance of adaptive immune response in controlling MNoV infection. We found that Rag1-/- mice lacking the B and T lymphocytes failed to clear the persistent MNoV infection as compared to wild type mice. Strikingly, we observed a dramatic resistant to MNoV in the Rag2/Il2rg-/- mice that lack natural killer cells along with the lymphocytes. This phenomenon was transferable to Rag1-/- mice by cohousing and fecal transplantation from Rag2/Il2rg-/- mice highlighting the presence of a microbial factor conferring resistance to MNoV. In addition, we detected elevated levels of Ifnl2/3 and ISGs such as Ifit1 in Rag2/Il2rg-/- mice as compared to wild-type and Rag1-/- mice that might contribute to resistance to MNoV infection. Our findings underline a unique commensal microbiota driven mechanism for resistance to MNoV persistence in immunodeficiency via transkingdom interactions.
Role of ISG15 in the Regulation of Programmed Cell Death

Yi-Chieh Perng

Perng YC, Young A, Morales D, Werneke S, Lenschow D

Internal Medicine
Faculty Mentor: Deborah Lenschow

ISG15 (interferon stimulated gene 15) is a ubiquitin-like protein which has been shown to limit viral replication, modulate immune response, and impact a variety of cellular activities. Previously we had reported that ISG15 involves in host disease tolerance by regulating the damage and/or repair of the respiratory epithelium following viral infection. However, the potential mechanism was unclear. We hypothesized that ISG15 controls programmed cell death to mediate disease tolerance. To test this, we applied ontology analysis to dissect cellular pathways of virally infected cells and found that ISG15 deficient cells displayed upregulation of cell death. However, ISG15 does not involves in caspase-dependent apoptosis. Instead, upon caspase inhibition, ISG15 deficient MEFs stimulated by either TNF or TLR ligands are more susceptible to cell death, displaying an early and more robust complex assembly composed of phospho-MLKL proteins, a representative marker of necroptosis. Consistent with this, such events could be rescued by necroptosis inhibitors, indicating ISG15 might negatively regulates necroptosis. By examining human and murine ISG15 deficient cells, we further confirmed that this activity is well conserved in both species. Notably, cells deficient in ISGylation conjugation enzyme do not exhibit similar necroptotic cell death as ISG15 deficient cells, indicating it is the free, unconjugated ISG15, but not protein ISGylation, modulates necroptosis. In summary, we identified a novel mechanism in which ISG15 serves as a negative regulator of necroptosis downstream of TNF or TLR signaling to prevent unnecessary cell death deteriorating tissue damage.
Intrinsic transcytosis pathway in brain endothelial cells mediates alphavirus neuroinvasion

Hamid Salimi

Internal Medicine
Faculty Mentor: Robyn Klein

Neurotropic alphaviruses including Venezuelan-, Western- and Eastern equine encephalitis viruses (VEEV, WEEV and EEEV, respectively) infect the central nervous system (CNS) as early as day one post infection. Defined mechanisms of alphavirus neuroinvasion are yet to be elucidated. Using in vitro and in vivo studies, we demonstrate that VEEV and WEEV are able to infect brain microvascular endothelial cells (BMECs), astrocytes and pericytes; cell types that form the blood brain barrier (BBB). Additionally, utilizing transmission electron microscopy (TEM), we have illustrated alphavirus transmigration across BMECs within intracellular vesicles characteristic of caveolae. These results were further confirmed using biochemical approaches, wherein inhibitors of caveolae but not clathrin or micropinocytosis inhibited virus transcytosis across BMECs using an in vitro BBB model. We have also established that exposure of BMECs to H-1152P (an inhibitor of RhoA GTPase) and type I IFNs restricts alphavirus transcytosis. Likewise, VEEV infection of IFNAR deficient mice resulted in massive virus replication in BMECs in different brain regions. Together, our results support the notion that CNS entry of alphavirus occurs via caveolae-mediated transcytosis in BMECs. These findings also highlight the role of type I IFNs in restricting viral replication and maintenance of the BBB integrity via effects on endocytic pathways within BMECs.
A multitude of circulating Loa loa antigens are responsible for cross-reactivity in rapid diagnostic tests for lymphatic filariasis

Marla Hertz


Internal Medicine - Infectious Diseases
Faculty Mentor: Philip Budge

Lymphatic filariasis (LF) is a debilitating and disfiguring infectious disease caused primarily by the parasitic filarial worm Wuchereria bancrofti. The Global Program to Eliminate Lymphatic Filariasis relies on rapid diagnostic tests (RDTs) to determine where annual mass drug administration for LF is required and when it can be stopped. These tests detect a secreted W. bancrofti glycoprotein in the blood of infected persons. The recent finding that some patients infected with a related filarial parasite, Loa loa, test falsely positive for LF is a serious obstacle to LF elimination in loiasis-endemic nations. To better understand the nature of loiasis cross-reactivity, L. loa antigens from the sera of individuals with a false positive W. bancrofti RDT were immunoaffinity purified using a monoclonal antibody that recognizes a carbohydrate epitope on the W. bancrofti circulating antigen (AD12). Surprisingly, western blot analysis revealed many AD12 cross-reactive antigens, and a proteomic analysis confirmed that greater than 200 L. loa proteins were present. These proteins are functionally diverse and included both secreted and somatic antigens. These data suggest that release of cross-reactive loiasis antigens arise from a process distinct from the secretion of a single antigen in bancroftian filariasis. Additionally, we found that O-sialoglycoprotein endopeptidase (OSGE), which cleaves negatively charged mucin-like glycoproteins, completely degraded cross-reactive L. loa antigens. Interestingly, OSGE did not degrade the W. bancrofti circulating antigen under the same conditions, suggesting the exciting possibility that pre-treatment of cross-reactive sera with OSGE or other proteases may improve the specificity of diagnostic tests for LF.
Genomic dissection of age-related differences in polycythemia vera

Jared Fowles

Fowles JS, How J, Oh ST

Internal Medicine
Faculty Mentor: Stephen Oh

Polycythemia vera (PV) is a type of myeloproliferative neoplasm (MPNs) that overproduces red blood cells and is driven by JAK2 V617F mutation-induced JAK-STAT signaling. Although commonly diagnosed in older individuals, PV can occur in younger patients which are associated with a different clinical profile, though the reasons for these associations are unclear. We hypothesized the mutational profile of younger PV would differ from older PV, which could contribute to the clinical differences observed.

DNA from bulk peripheral blood mononuclear cells and matched normal tissue (skin or sorted CD3+ T cells) were isolated from 10 patient samples 45 years and younger and 11 patients 65 years and older. Enhanced exome capture sequencing targeting all exons plus additional probes for AML and MPN-specific genes was performed.

We identified 103 mutations overall. A higher mutational load was observed in older PV (p = 0.0025, Mann-Whitney), as well as for AML/MPN specific genes (p = 0.009). Strikingly, putative secondary driver mutations were identified in 9/10 older PV patients, whereas in all younger PV patients JAK2 appeared to be only driver mutation present. Inferring from variant allele frequencies it appeared that 5/9 patients acquired a secondary mutation after JAK2.

Our data suggests the mutational profile between young and old PV is different. The increase of mutations in older PV patients complies with age-related accumulation, but the majority of older PV mutations occurring after JAK2 suggest they are not independent from PV development/progression. Questions remain how a single driver landscape can contribute to the clinical differences seen in the younger population, which suggests germline or non-genomic factors yet to be elucidated.
Identifying and Disarming the Malignant Epigenome of Glioblastoma

Devi Annamalai

Annamalai D, Kim A

Neurosurgery
Faculty Mentor: Albert Kim

Epigenetic alterations have been shown to majorly contribute to tumor-forming potential in Glioblastoma (GBM), the most common malignant brain tumor in adults. A subpopulation of GBM cells, called “tumor-initiating cells” (TIC, also GBM stem-like cells) has the ability to propagate tumors in vivo and exhibit resistance to standard therapies. Although malignancy-driving epigenome modifications have been observed in GBM, the molecular mechanisms underlying these modifications have not been well-characterized and effective strategies to alter the malignant GBM molecular status remains unexplored. We have been examining the therapeutic potential of altering the GBM epigenome through direct reprogramming. Through the regulation of epigenetic pathways, microRNAs play a critical role in cancer initiation, maintenance and progression. Recently, Yoo and colleagues demonstrated that human skin fibroblasts could be converted into post-mitotic neurons through forced expression of microRNAs 9/9* and 124 (miR 9/9*/124), which are important for normal nervous system development. Remarkably, lentiviral overexpression of miR 9/9*/124 in human GBM TICs led to cell cycle exit within 3 days and evidence of neuronal differentiation within 7 days. Preliminary experiments using an orthotopic xenograft model demonstrated increased survival in mice injected with miR 9/9*/124-expressing TICs compared to mice injected with control-infected TICs, suggesting miR-induced reprogramming inhibits the GBM tumor-initiating state. We are currently characterizing the epigenetic landscape of miR 9/9*/124-expressing TICs to uncover the mechanism of miR-induced conversion of TICs to a non-tumorigenic state.
Tumor suppressors p53 and ARF control oncogenic potential of triple-negative breast cancer cells by regulating RNA editing enzyme ADAR1

Che-Pei Kung

Kung CP, Bross EA, Kuzmicki CE, Benjamin ML, Maggi LB Jr., Weber JD

Internal Medicine
Faculty Mentors: Jason Weber and Leonard Maggi Jr

Triple-negative breast cancer (TNBC) accounts for one-fifth of the breast cancer patient population. The heterogeneous nature of TNBC and lack of options for targeted therapy make its treatment a constant adventure. The deficiency of tumor suppressors p53 and ARF is one of the known genetic signatures enriched in TNBC. Crucial questions remain about how TNBC is regulated by these genetic alterations. In order to address this issue, we established p53/ARF-defective murine embryonic fibroblast (MEF) and mammary epithelial cell (MMEC) to study the molecular and phenotypic consequences. Moreover, transgenic mice were generated to investigate the effect of p53/ARF deficiency on mammary tumor development in vivo. Increased proliferation and transformation capability were observed in p53/ARF-defective cells, and an aggressive form of mammary tumor was also seen in p53-/-ARF-/- mice. Gene expression profiling and knock-down experiments using shRNAs were conducted to identify inflammatory marker ISG15 and RNA-editing enzyme ADAR1 as potential culprits for the elevated oncogenic potential. Interestingly, we found that the overexpression of ISG15 and ADAR1 is also prevalent in human TNBC cell lines. Reducing ADAR1 expression abrogated the oncogenic potential of human TNBC cell lines, while non-TNBC cells are less susceptible. These results indicate critical roles played by the tumor suppressors p53 and ARF in the pathogenesis of TNBC, likely through regulating ADAR1-mediated RNA modifications. Further understanding of this pathway promises to shed light on genetics-driven vulnerabilities of TNBC and inform development of more effective therapeutic strategies.
Comparative genomics provides insight into the evolution of parasitic flatworms in the family Fasciolidae

Young-Jun Choi

Choi Y, Fischer PU, Brindley PJ, Tort JF, Cabada MM, Mitreva M

McDonnell Genome Institute
Faculty Mentor: Makédonka Mitreva

The liver and intestinal flukes in the family Fasciolidae cause zoonotic food-borne infections that have a substantial impact on both agriculture and human health throughout the world. Here, we present a comparative genomic analysis of Fasciola hepatica, Fasciola gigantica, and Fasciolopsis buski with the aim to better understand their evolutionary history and the genetic bases underlying their phenotypic and ecological divergence. Molecular dating reveals that the split between the genus Fasciolopsis and Fasciola took place around 90 Ma in the late cretaceous period, and between 65 and 50 Ma, an intermediate host switch and a shift from intestinal to hepatic habitats occurred in the Fasciola lineage. The rapid climatic and ecological changes that occurred during this period (e.g., K-Pg mass extinction and Paleocene-Eocene Thermal Maximum) may have contributed to the adaptive radiation of these flukes. Analysis of gene family dynamics indicates an expansion in cathepsins, legumains, and fatty acid binding proteins in Fasciola spp. suggesting their likely role in the lineage-specific adaptation. Our data show that the divergence between F. hepatica and F. gigantica occurred around 5 Ma near the Miocene-Pliocene boundary that coincides with a reduced faunal exchange between Africa and Eurasia, which may have contributed to the speciation process. Estimates of historical F. hepatica population size indicate a severe decrease in the effective population size around ~10 Ka, consistent with its recent global spread associated with the ruminant domestication. Genome-wide analysis of selection signatures in Fasciola reveals that G-protein-coupled receptors are under positive and/or relaxed purifying selection, suggesting their significance in the parasite’s adaptive evolution.
Mouse Embryonic Fibroblasts Protect ob/ob Obese Mice from Metabolic Phenotypes

Daniel Ferguson

Ferguson D, Blenden M, Hutson I, Du Y, Harris C

Internal Medicine - Endocrinology and Metabolism
Faculty Mentor: Charles Harris

The global obesity epidemic is fueling alarming rates of diabetes, associated with increased cardiovascular disease and cancer risk. Leptin is a hormone secreted by adipose tissue that is a key regulator of body weight and energy expenditure. Leptin-deficient humans and mice are obese, diabetic and have fatty liver. Patients with generalized lipodystrophy (LD), a condition characterized by the absence of adipose tissue, have very low leptin levels resulting in severe insulin resistance and hepatic steatosis. While leptin replacement can rescue the pathologies seen in LD patients and leptin-deficient ob/ob mice, treatment is costly and requires daily injections. Since adipocytes are the source of leptin secretion we tested if mouse embryonic fibroblasts (MEFs), capable of forming adipocytes, could be injected into ob/ob mice and prevent the metabolic phenotype seen in these leptin-deficient mice. To do this we performed a single subcutaneous injection of MEFs into male ob/ob mice at 3 weeks of age. The MEF injection formed a single large fat pad which is histologically similar to white adipose tissue. The ob/ob mice receiving MEFs, referred to as ob rescue (obR), had significantly reduced body weight compared to ob/ob mice, primarily due to a decrease in adipose tissue. Additionally, obR mice had significantly reduced liver size and liver triglycerides compared to ob/ob. Improvement in metabolic endpoints in obR versus ob/ob mice was likely due to decreased food intake and increased energy expenditure. Collectively, our studies show the importance of functional adipocytes in preventing metabolic abnormalities seen in leptin deficiency and point to the possibility of cell-based therapies for the treatment of leptin-deficient states including LD.
Different effects of biliopancreatic diversion and Roux-en-Y gastric bypass on postprandial plasma metabolites

Brandon Kayser

Kayser BD, Harris LA, Mohit J, Mingrone G, Klein S

Internal Medicine - Nutrition Sciences
Faculty Mentor: Samuel Klein

We recently found that weight loss induced by biliopancreatic diversion (BPD) caused a greater improvement in insulin sensitivity than the same weight loss induced by Roux-en-Y gastric bypass (RYGB). The purpose of this study was to identify whether there are also potential beneficial effects of BPD-induced weight loss on the plasma metabolite response to a mixed meal. Blood samples were obtained before (time 0) and at 30, 60, 120, 180, 240, 300 and 360 min after ingesting a liquid mixed meal (72% CHO, 14% fat and 14% protein) before and after 20% weight loss induced by RYGB (n=12) or BPD (n=12) in people with obesity. Untargeted metabonomics were performed using sophisticated liquid chromatography-mass spectrometry techniques. Linear mixed effects models were used to determine differences in postprandial metabolites between surgery groups. Weight loss after both RYGB and BPD caused similar changes in 87 postprandial plasma metabolites, whereas the change in 50 metabolites were different between surgery groups. Compared with the data obtained before surgery: 1) plasma glucose rose and fell more rapidly after RYGB, while the glucose excursion was blunted following BPD; 2) 18 plasma free fatty acids decreased more with RYGB; 3) primary conjugated and unconjugated bile acids increased with RYGB but decreased with BPD; and 4) amino sugars (glucosamine and galactosamine) increased with RYGB, but decreased with BPD. We conclude that compared with RYGB, matched weight loss induced by BPD causes marked differences in the plasma metabolite response to mixed meal ingestion. Additional studies are needed to determine whether one or more of the differences in these metabolites contribute to the greater improvements in insulin sensitivity seen after BPD.
Increased Uncoupled Respiration Of Subcutaneous White Adipose Tissue Is Linked To Systemic Changes In Glucose And Lipid Metabolism In Humans

Maria Chondronikola

Chondronikola M, Herdon DN, Porter C, Sidossis LS

Internal Medicine Nutritional Sciences
Faculty Mentor: Samuel Klein

Prolonged adrenergic stimulation induces the browning of subcutaneous white adipose tissue (WAT), which is thought to improve metabolic control in rodents. This study evaluated the relationship between browning of WAT and glucose and free fatty acid (FFA) metabolism in humans. Burn injury represents a unique human model of browning of WAT, since WAT undergoes browning about two weeks after severe burn injury. To this end, we studied patients with severe burns the first and third week after admission to the hospital for acute burn care. Patients were randomized to receive the non-selective β-blocker propanol (PPL, n=9) or placebo (CON, n=11) during hospitalization. We hypothesized that the browning of WAT would positively correlate with whole body glucose disposal and adipose tissue lipolysis in the CON group, while β-adrenergic blockade would abolish this relationship in the PPL group. Infusion of stable isotopes was used to determine FFA and glucose kinetics in vivo. WAT samples collected during surgery were assessed using high-resolution respirometry. The oligomycin-insensitive uncoupled respiration rate was used as a functional index of browning of WAT. WAT uncoupled respiration increased with time (CON: 0.6±0.3 vs. 1.3±0.5 pmol/s/mg, PPL: 0.5±0.4 vs.1.3±0.6 pmol/s/mg, p=0.003). The change in WAT uncoupled respiration from the first to the third week post burn correlated positively with the change in adipose tissue lipolysis (r=0.745, p=0.008) and whole-body glucose disposal (r=0.661, p=0.038) in the CON group, but not in the PPL group. These data demonstrate the link between WAT uncoupled respiration and whole-body glucose and FFA kinetics. Further, they suggest that browning of WAT could affect glucose and FFA metabolic control in the whole body level in humans.
Dapagliflozin, a sodium-glucose transporter 2 (SGLT2) inhibitor, restores β-cell function and mass in severely diabetic mice

Zeenat Asghar Shyr

Shyr ZA, Yan Z, Ustione A, Piston DW, Remedi MS

Medicine
Faculty Mentor: Maria Remedi

Progressive loss of pancreatic β-cell function and mass are classic findings in diabetes. Loss of β-cell mass and function have been attributed to membrane hyperexcitability and insulin hypersecretion. However, we demonstrated a marked loss of β-cell mass in an insulin secretory deficient KATP-gain of function (KATP-GOF) mouse model of human neonatal diabetes in which these factors are absent. Islets from diabetic KATP-GOF mice show increased glucose metabolism and oxygen consumption rate, accompanied by a marked increase in oxidative and ER stress markers. We show that loss of insulin content/β-cell mass, and therefore antidiabetic drug responsivity, can be restored by lowering blood glucose levels by insulin therapy; however, it remains unknown whether hyperglycemia per se or lack of insulin is the causative factor. We hypothesized that if hyperglycemia plays a dominant role, lowering blood glucose alone would be sufficient to prevent loss of β-cell mass and improve β-cell function. To test this, we treated diabetic KATP-GOF mice with dapagliflozin, a sodium-glucose transporter-2 inhibitor clinically used to reduce blood glucose levels by preventing renal glucose reabsorption. Dapagliflozin significantly reduced blood glucose levels by increasing urinary glucose excretion without changing circulating insulin levels. Strikingly, 10 days of dapagliflozin therapy markedly restored insulin content and improved β-cell function by alleviating cellular oxidative and ER stress. We demonstrate that β-cell failure and loss of β-cell mass is reversible, and that reduction of blood glucose alone is sufficient to prevent the progressive β-cell dysfunction and failure, thus providing an exciting prospect for the prevention of diabetes progression.
Mapping Hot Spots of Breast Cancer Mortality in the United States: Place Matters for Blacks and Hispanics

Justin Xavier Moore


Department of Surgery
Faculty Mentors: Graham Colditz and Aimee James

PURPOSE: The goals of this study were to evaluate geographic and racial/ethnic variation in breast cancer mortality, and evaluate whether observed geographic differences are explained by community characteristics.

METHODS: We analyzed data on breast cancer deaths among women in 3108 contiguous United States (US) counties from years 2000 through 2015. We applied novel geospatial methods and identified hot spot counties based on breast cancer mortality rates. We assessed differences in community characteristics between hot spot and other counties using Wilcoxon rank-sum test and Spearman correlation, and stratified all analysis by race/ethnicity.

RESULTS: Among all women, 80 of 3108 (2.57%) contiguous US counties were deemed hot spots for breast cancer mortality with the majority located in the southern region of the US (72.50%, p value < 0.001). In race/ethnicity-specific analyses, NH-Black women resided in 119 (3.83%) hot spot counties, with the majority being located in southern states (98.32%, p value < 0.001). Among Hispanic women, there were 83 (2.67%) hot spot counties and the majority was located in the southwest region of the US (southern = 61.45%, western = 33.73%, p value < 0.001). We did not observe definitive geographic patterns in breast cancer mortality for NH-White women. Hot spot counties were more likely to have residents with lower education, lower household income, higher unemployment rates, higher uninsured population, and higher proportion indicating cost as a barrier to medical care.

CONCLUSIONS: We observed geographic and racial/ethnic disparities in breast cancer mortality: NH-Black and Hispanic breast cancer deaths were more concentrated in southern, lower SES counties.
The Geography of Sickle Cell Disease: Neighborhoods, Healthcare, & Education

Kelly Harris

Harris KM

Program in Occupational Therapy
Faculty Mentor: King, Allison

Chronic conditions have become increasingly common among youth, particularly in racial and ethnic minorities and in lower income households. Youth with chronic diseases face additional barriers to completing their education, a crucial gateway to accessing opportunities for higher paying jobs, desirable neighborhoods, and improved health. Children with sickle cell disease (SCD), an inherited disorder predominantly impacting African Americans, are particularly vulnerable, as the disease is associated with chronic anemia, frequent pain episodes that result in missed school days, and stroke. In addition, almost 70% of children with SCD are living near poverty. Following an ecological model, this study constructs a state population-based cohort incorporating medical claims history, neighborhood, school, and district characteristics to examine the relationships between health disparities, education, and neighborhoods. Initial analysis uses Geographic Information Systems (GIS) to determine the associations between neighborhood level characteristics (e.g. income, race, crime, housing, and physical access to healthcare services), school level characteristics (e.g. attendance, assessment scores, and school completion measures), healthcare utilization (e.g. emergency room visits and hospitalizations), disease modifying prescriptions, and routine care by a primary care physician (PCP) for youth with SCD. Multi-level models examine the relationship between neighborhood and school characteristics and the number and type of medical claims, disease modifying prescriptions, and routine medical care for youth with SCD. Results reveal associations between SCD, healthcare utilization, and geography, and inform practice solutions improve education and preventative care for youth with SCD.
Childhood Risk Factors to Early Onset Cannabis Use Among African-American and European-American Adolescents

Manik Ahuja

Ahuja M, Bucholz KK

Psychiatry
Faculty Mentors: Kathleen Bucholz and Renee Cunningham-Williams

AIMS: Familial factors during early childhood including parental substance misuse contribute to increased risk for cannabis use in offspring, but whether they increase risk for early use is not well studied. We focused on associations of familial factors and family risk (1) to test the association of a familial factors from age 6 to 13 including family rearing environment, parental discipline, and parental substance misuse (2) improve our understanding of how risk factors during adolescence for early cannabis use may vary by race and gender.

METHODS: Data (n=1,461) are from the Missouri Family study (MOFAM), a longitudinal high-risk family study designed to examine the effects of familial influences on adolescent offspring outcomes including alcohol, tobacco, and illicit drug involvement in a sample of ethnically diverse families. Multivariate analysis were used to determine the association between familial factors and early cannabis use. Analyses were stratified by race.

RESULTS: In the African American cohort, Parent separation/divorce (RRR=2.66; 95% CI:1.26-4.01), two or more forms of childhood physical discipline (RRR=2.24; 95% CI: 1.23-4.08), physical discipline (mother) that hurt the next day (RRR=1.80; 95% CI: 1.00-3.23), and conduct disorder symptoms (RRR=5.89; 95% CI: 3.27-10.62) were associated with early onset of cannabis use before age 15. In the European American cohort, maternal and paternal cannabis use (RRR=4.75; 2.21-10.19) and (RRR= 3.2; 95% CI: 1.31-7.87) respectively and conduct disorder symptoms (RRR=3.44; 1.42-8.34) were associated with early cannabis use.

CONCLUSION: Key differences in risk factors for early cannabis use were found at the race level. It is critical that further research be conducted to understand underlying pathways.
Overview of the CIViC database for clinical interpretations of variants in cancer

Arpad Danos

Danos AM, Krysiak K, Spies NC, Coffman AC, McMichael JF, Kiwala S, Wagner AH, Barnell EK, Griffith M, Griffith OL

McDonell Genome Institute
Faculty Mentors: Obi Griffith and Malachi Griffith

With the growing availability of cancer genome sequencing coupled with increasing knowledge associated with the many thousands of variants seen in cancer, there is great need for databases which focus on that subset of variants which have concrete clinical or preclinical data associated to them. Construction of databases of this sort is labor intensive, requiring massive amounts of curation effort. Some databases hold this curated knowledge behind paywalls, presumably using fees to pay for curation effort. Another approach is crowdsourcing curation effort, which allows the database to be a free publicly available resource, able to continually grow and remain updated with the latest findings on cancer variants from clinical trials and basic research. The Clinical Interpretations of Variants in Cancer (CIViC) database is designed to function in this manner, and has to date built a community of over 100 contributing members and over 16,000 users from research and clinical institutions worldwide.

The fundamental unit of knowledge in CIViC is the evidence item (EID). The EID associates a predictive, prognostic, diagnostic or predisposing statement to a specific variant and specific cancer type using evidence derived from peer-reviewed publications and linked to Pubmed ID. EIDs associated with a specific variant are grouped together, and clinical assertions for that variant can be made when the quantity and quality of evidence is sufficient. Cancer community guidelines (ACMG and AMP) for variant classification are built into assertion structure. Multiple collaborations are underway including integration of an existing VHL gene database into CIViC, a large import of variant data from Illumina, and development with ClinGen of a workflow for CIViC submission to ClinVar.
Novel small-molecule biomarkers of bladder pain syndrome

John Robinson


Medicine
Faculty Mentor: Jeffrey Henderson

Bladder pain syndrome (BPS) in women and chronic pelvic pain syndrome (CPPS) in men are poorly-understood chronic pain conditions affecting a significant number of adults in the U.S. Without objective diagnostics or a clear understanding of disease etiology, it remains difficult to both diagnose and treat BPS and CPPS. Previously, the Henderson lab employed an unbiased mass-spectrometry-based metabolomics approach to screen urine samples from healthy and BPS women for small-molecule predictors of BPS. This work uncovered two distinct populations of BPS patients and identified a sulfated steroid and a set of related metabolites that reliably discriminate BPS patients from healthy patients. Here, I extend this work to include male CPPS patients. Unbiased urinary metabolome characterization of these patients identified distinct metabolic profiles correlated with mild or severe pain in CPPS patients and separate from healthy patient profiles. From these metabolic profiles, several currently-unidentified metabolites each accurately distinguish the three patient groups. Taken together, these metabolites represent promising candidates for positive diagnosis of BPS and CPPS. Furthermore, they may well provide a window into the pathology of BPS and CPPS.
Fibrosis Quantitation in Post-Transplant Renal Biopsies

Matthew Williams

Williams MJ, Dharnidharka VR, Hruska KA

Pediatrics
Faculty Mentor: Keith Hruska

Kidney transplant is the best treatment for End Stage Renal Disease, but half-life of the allograft following deceased donor transplantation is only 8 years. The process describing progressive loss of function of kidney allograft in the absence of acute rejection is called interstitial fibrosis and tubular atrophy (IF/TA), and is partially identified by the presence of interstitial fibrosis in histological sections. In a preclinical model of chronic kidney disease, we have shown the inhibition of activin receptor signaling significantly reduces interstitial fibrosis. Therefore, it is our overall hypothesis that the process driving IF/TA in post-transplant allografts is analogous to that observed in chronic kidney disease. One key requirement to examine this relationship is accurate quantitation of interstitial fibrosis. Traditionally, a pathologist grades level of severity of fibrosis by estimation of affected area in stained biopsy sections, but it is not continuous and subject to individual interpretation. One approach for semi-automated quantitation of renal fibrosis has been introduced for mouse kidney histology; it utilizes polarized light imaging of tissue sections stained with Picrosirius red. We examined whether this method could be adapted for use in quantifying fibrosis in human biopsies. Multiple scripts were developed to facilitate the stitching of irregular-shaped biopsies into composite images, identify regions of interest, and determine percent fibrosis. The quantitation of fibrosis of 81 post-transplant kidney biopsies from 33 patients ranged from .5% to 11% area coverage and progression was in agreement with pathologist scoring. The next step is to correlate these results with kidney function and markers of activin receptor signaling.
Diffusion-weighted imaging of the kidney: Effect of respiratory gating and ADC calculation approach

Xue Wu

Xue Wu, Hao Song, Pohmann  R, Stenger VA, Luo J, Gach HM

Radiation Oncology
Faculty Mentor: Michael Gach

Molecular self-diffusion is an important biomarker for cancer and organ function. Diffusion-weighted imaging (DWI) magnetic resonance imaging (MRI) is used to monitor disease progression and treatment response. However, the apparent diffusion coefficient (ADC) can vary based on the MRI protocol and data fitting calculation methods. Respiratory motion, ghosting, and chemical shift artifacts may also affect the ADC values. This study evaluated two different ADC calculation approaches and the effect of motion compensation for renal DWI. Twelve healthy volunteer (age of 26+-1.4 years) were scanned as part of a renal perfusion MRI study. Diffusion-weighted images were acquired at 3 T in 3 directions with and without respiration motion compensation. ADC values were calculated by a linear fitting approach with two b value pairs (0, 500 and 0, 1000), and a two-parameter fitting approach with three b values (0, 500, and 1000).

In the linear fitting approach, average ADCs with respiratory gating were 0.0022 +/- 0.0003 mm²/sec using b values 0 and 500, and 0.0012 +/-0.0002 mm²/sec using b values 0 and 1000. The ADCs without respiratory gating were 0.0024 +/- 0.0004 mm²/sec using b values 0 and 500 and 0.0013 +/-0.0002 mm²/sec using b values 0 and 1000. In the two-parameter fitting approach, average ADCs were 0.0023 +/- 0.0005 mm²/sec with respiratory gating and 0.0024 +/- 0.0005 mm²/sec without respiratory gating. All of the ADCs were within the range of previous studies. There were significant differences in ADC values using different b values (p < 0.01). However respiratory gating did not have significant effect on the ADC values in both calculation approaches (p > 0.05).
Thank You!

Dr. Jennifer Lodge · Dr. John Russell · Dr. Jessica Hutchins

Faculty Poster Judges
Dr. Kareem Azab · Dr. Luis Batista · Dr. Milan Chheda
Dr. Mark J. Miller · Dr. Zachary Pincus · Dr. Christina Stallings

Symposium Committee
Dr. Maria Chondronikola · Dr. Carissa Dege · Dr. Mitch D’Rozario
Dr. Bailey Fearing · Dr. Kristen Funk · Dr. Reza Ghasemi
Dr. Natalia Harasymowicz · Dr. Nelly Joseph-Mathurin
Dr. Brigida Rusconi · Dr. Molly Sutherland · Dr. Elias Tannous
Dr. Francisco Victorino

Washington University Postdoc Society
2017/2018 Executive Council Officers
President: Francesca Cignarella, cignarella.f@wustl.edu
Vice President: Francisco Victorino, ramirezvictorino@wustl.edu
Secretary: Carissa Dege, carissadege@wustl.edu
Treasurer: Daniel Agustinho, danielagustinho@wustl.edu
Publicist: Vipul Sharma, v.sharma@wustl.edu
Danforth Representative: Bailey Fearing, baileyfearing@wustl.edu

Office of Postdoctoral Affairs
Dr. Erin Heckler · Dr. John Russell

If you do not need your name badge or program, please return it to the registration desk for recycling.
Thank you!
## Poster Presenters & Resource Fair

<table>
<thead>
<tr>
<th>PRESENTER (POSTER #)</th>
<th>Pg.</th>
<th>PRESENTER (POSTER #)</th>
<th>Pg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manik Ahuja (34)</td>
<td>1</td>
<td>Brandon Kayser (6)</td>
<td>18</td>
</tr>
<tr>
<td>Devi Annamalai (26)</td>
<td>2</td>
<td>Che-Pei Kung (19)</td>
<td>19</td>
</tr>
<tr>
<td>Zeenat Asghar Shyr (7)</td>
<td>3</td>
<td>Dandan Liu (24)</td>
<td>20</td>
</tr>
<tr>
<td>Mathieu Bottier (31)</td>
<td>4</td>
<td>Yongfeng Liu (21)</td>
<td>21</td>
</tr>
<tr>
<td>Young-Jun Choi (3)</td>
<td>5</td>
<td>Sidhartha Mahali (32)</td>
<td>22</td>
</tr>
<tr>
<td>Maria Chondronikola (2)</td>
<td>6</td>
<td>Pallavi Malavi (14)</td>
<td>23</td>
</tr>
<tr>
<td>Arpad Danos (17)</td>
<td>7</td>
<td>Jana Markley (1)</td>
<td>24</td>
</tr>
<tr>
<td>Daniel Ferguson (33)</td>
<td>8</td>
<td>Tanumoy Mondol (25)</td>
<td>25</td>
</tr>
<tr>
<td>Jared Fowles (30)</td>
<td>9</td>
<td>Justin Xavier Moore (15)</td>
<td>26</td>
</tr>
<tr>
<td>Benjamin Gerovac (11)</td>
<td>10</td>
<td>Yi-Chieh Perng (28)</td>
<td>27</td>
</tr>
<tr>
<td>Joseph Griffis (4)</td>
<td>11</td>
<td>Keith Rennier (18)</td>
<td>28</td>
</tr>
<tr>
<td>Alexandra Halevi (20)</td>
<td>12</td>
<td>John Robinson (9)</td>
<td>29</td>
</tr>
<tr>
<td>Kelly Harris (5)</td>
<td>13</td>
<td>Hamid Salimi (10)</td>
<td>30</td>
</tr>
<tr>
<td>Marla Hertz (29)</td>
<td>14</td>
<td>Husain Shekhani (12)</td>
<td>31</td>
</tr>
<tr>
<td>Panpan Hou (8)</td>
<td>15</td>
<td>Molly Sutherland (22)</td>
<td>32</td>
</tr>
<tr>
<td>Harshad Ingle (13)</td>
<td>16</td>
<td>Matthew Williams (23)</td>
<td>33</td>
</tr>
<tr>
<td>Hongmei Jiang (16)</td>
<td>17</td>
<td>Xue Wu (27)</td>
<td>34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RESOURCE PARTNER</th>
<th>Pg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washington University Postdoctoral Society (WUPS)</td>
<td>11</td>
</tr>
<tr>
<td>The Office of Postdoctoral Affairs (OPA)</td>
<td>11</td>
</tr>
<tr>
<td>Biotechnology and Life Sciences Advising Group (BALSA)</td>
<td>12</td>
</tr>
<tr>
<td>Clinical Research Training Center (CRTC) TL1</td>
<td>12</td>
</tr>
<tr>
<td>Translational Sciences Postdoctoral Program (TSPP)</td>
<td>12</td>
</tr>
<tr>
<td>English Language Programs (ELP)</td>
<td>13</td>
</tr>
<tr>
<td>Future Educators</td>
<td>13</td>
</tr>
<tr>
<td>InPrint - A scientific editing network</td>
<td>13</td>
</tr>
<tr>
<td>The Office of the Ombuds</td>
<td>14</td>
</tr>
<tr>
<td>Sling Health</td>
<td>14</td>
</tr>
<tr>
<td>The Teaching Center</td>
<td>15</td>
</tr>
<tr>
<td>The Office of the Vice Chancellor for Research (OVCR)</td>
<td>15-16</td>
</tr>
</tbody>
</table>