

**University of Virginia
School of Medicine
Faculty Research Retreat**

**The Boar's Head Inn
Charlottesville, VA
February 8 – 9, 2013**

**University of Virginia School of Medicine
2013 Faculty Research Retreat**

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| Boar's Head Inn (including location of parking lots) | |
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Registration table, contacting event administrative staff

Registration will open on Friday at 2:00 PM in the Pavilion. The registration table will be staffed through midday on Saturday. Steve Wasserman cell phone: 434-989-1255

Parking

You may park in any of the gray lots marked on the [map of the Boar's Head](#) found later in this document. There is a handicapped parking space outside the main entrance to the Pavilion.

Acknowledgments

We wish to thank Joyce Fortune, Johy Betts, Ashley Ayers and Kathleen Foster for their administrative support leading up to and during this event.

**University of Virginia School of Medicine
2013 Faculty Research Retreat
Schedule of events**

| Day | Time | Activity | Session/participants | Location |
|-----------------|--------------------|---|---|--|
| Friday | 3:00-6:00 PM | Posters, reception | Poster session 1 and opening reception | Pavilion, Ednam |
| | 6:30-7:30 PM | Dinner | | Pavilion (combined) |
| | 7:30-8:30 PM | Speaker | Translational Research: the grand challenges William N. Hait, MD, PhD Global Head Janssen Research & Development Johnson & Johnson | |
| Saturday | 7:30-8:00 AM | Breakfast | <i>(bring your breakfast into your first concurrent session)</i> | Pavilion I, II, III |
| | 8:00-10:00 AM | Concurrent sessions | <u>New Frontiers of Genetics and Epigenetics in Human Disease</u> (Dutta, Hall, Adli, Li, discussants [Moskaluk, Turner, Rich, Mahadevan]) | Pavilion I |
| | | | <u>Collaborative Approaches to the Study of Complex Disease: Hypertension and Stroke</u> (Felder, Siragy, Johnston, Worrall) | Pavilion II |
| | | | <u>Translational Imaging at UVA: From Bench to Bedside</u> (Kramer, Bilchick, Druzgal, Tustison, Kelly) | Pavilion III |
| | 10:00-10:15 AM | Break | | |
| | 10:15 AM-12:15 PM | Concurrent sessions | <u>The Pathogenesis of Asthma: from Epidemiology to the Single Cell</u> (Platts-Mills, Heymann, Teague, Wisniewski) | Pavilion I |
| | | | <u>Brain Immunology and Glia: the New Frontiers in Translational Neuroscience</u> (Kipnis, Gaultier, McConnell, Lee) | Pavilion II |
| | | | <u>Translating Mathematics into Medicine: Systems Biology at UVA</u> (Papin, Kasson, Janes, Saucerman) | Pavilion III |
| | 12:15-1:45 PM | Lunch roundtable discussions | Eleven sessions are being offered (grab a lunch in the Pavilion and head to your session of choice) | <u>Various locations</u> |
| | 1:45-3:45 PM | Concurrent sessions | <u>Collaborations Leading to Innovations: Cardiovascular Research at UVA</u> (Owens, Ailawadi, McNamara, Isakson) | Pavilion I |
| | | | <u>New Frontiers and Opportunities for Collaboration in Neuro-Oncology</u> (Schiff, Abounader, Price, Zong) | Pavilion II |
| | | | <u>Understanding human biology during infection and inflammation - and - Lessons learned about research careers from young and senior investigators</u> (Petri, Criss, Tamm, Hughes) | Pavilion III |
| 3:45-4:00 PM | Break | | | |
| 4:00-6:00 PM | Posters, reception | Poster session 2 and closing reception | Pavilion, Ednam | |

University of Virginia School of Medicine
2013 Faculty Research Retreat
Concurrent sessions (to be held in the Pavilion)

Concurrent sessions 1: 8:00 – 10:00 AM (Pavilions I, II, and III)

Session 1a (Pavilion 1):
NEW FRONTIERS OF GENETICS AND EPIGENETICS IN HUMAN DISEASE

Chair and first speaker – Anindya Dutta

Introduction to state of current genomics research – discovery science, current clinical implications

ENCODE work indicates relatively few genes, but most of the genome is active – different types of RNA produced

Topic: Using ultra-high throughput sequencing to discover different types of nucleic acids and genomic information

Sequence, structural, and functional information, i.e., microRNAs (mRNA silencing), microDNAs (unknown function), tRNA fragments (cell proliferation control)

Future potential and directions

Ira Hall – DNA genomics

Extent, origin and control of structural variation in mammalian genomes

Structural variation in in genomes – normal and cancer cells

DNA from tumors suggests novel structural changes, novel oncogenes and tumor suppressors (Current status in tumors?)

Hui Li – Trans-splicing of RNA

New fusion proteins formed by trans-splicing of RNA between genes – normal and cancer cells

Higher levels in cancer – may contribute to tumor biology

Mazhar Adli – Epigenetics in the hematopoietic system

Epigenomic studies in hematopoietic cells – as few as 10,000 cells sufficient for surveying the epigenome

Role of epigenetic changes in stem cell differentiation, cancer

Stephen Rich – Genetic variations associated with disease in human populations

Panel Discussion/Answers to Questions

Discussants: C. Moskaluk, S Turner, S Rich, M. Mahadevan

Resources at UVA – BTRF, Bioinformatics, Genomics and Clinical Partners

**Session 1b (Pavilion II):
COLLABORATIVE APPROACHES TO THE STUDY OF COMPLEX DISEASE STATES:
HYPERTENSION AND STROKE**

Session description: The objective is to highlight approaches to studying hypertension and stroke at UVA. The following items will be discussed: the importance of a partnership between clinical and basic research; ways of approaching important research questions when large numbers of patients are required for reliable answers; and the use of new technologies (e.g., genomics) to answer important research questions.

Talk 1: Overview – Helmy Siragy – Approaching the complex and the enigmatic: hypertension and stroke as prismatic examples

Dr. Siragy will highlight the global impact of hypertension and stroke, describe some major questions and challenges, the benefits of local and national collaborations, in addition to new technologies/approaches (e.g., genomics).

Talk 2: Research – Robin Felder – Discovering the pathogenesis of essential hypertension and salt sensitivity: a multidimensional approach

Dr. Felder is spearheading a Program Project Grant designed to investigate mechanisms of salt sensitivity as it relates to blood pressure control. They are employing a multipronged approach including molecular genetics, biochemical techniques, in-vitro, and in-vivo studies in humans (collaboration with Bob Carey).

Talk 3: Research – Karen Johnston – Approach to hyperglycemia in acute ischemic stroke: the SHINE trial

Dr. Johnson is the National PI for the Stroke Hyperglycemia Insulin Network Effort (SHINE) Trial is a large, randomized, controlled, multicenter (over 60 US sites) phase III efficacy trial of intensive insulin therapy versus standard care for hyperglycemic acute ischemic stroke patients (funded by the NIH-NINDS). This effort involves endocrinology and a private sector entity that has the FDA-cleared decision support tool. Dr. Johnston could potentially discuss how this multicenter study was initiated and organized, how/why she was appointed national PI, the relationship with the private sector entity mentioned above, etc.

Talk 4: Research – Bradford Worrall – Understanding the links between intracranial and abdominal aortic aneurysms

The Brain and Aortic Aneurysm Study is a collaborative research program comprising the UVA Divisions of Vascular Neurology (Worrall, Southerland), Vascular Surgery (Upchurch), and the Center For Public Health Genomics in an effort to prospectively identify the co-prevalence of intracranial aneurysms (IA) and abdominal aortic aneurysms (AAA) in our patient population. These entities (IA and AAA) share a co-prevalence in a high risk subset of the population with common genetic and environmental risk factors. The following will be performed as pilot studies: (1) aortic sonography in participants with known IA, both ruptured and unruptured; (2) non-invasive vascular imaging (CTA or MRA) in participants with known AAA; and (3) genetic screening for high-risk variants associated with aneurysm formation. This research program provides the infrastructure for an ongoing multi-disciplinary, Brain and Aortic Aneurysm Clinic, to identify and properly manage high risk aneurysm patients going forward.

**Session 1c (Pavilion III):
TRANSLATIONAL IMAGING AT UVA: FROM BENCH TO BEDSIDE**

Cardiovascular Imaging

Christopher Kramer – Cardiovascular Imaging at UVA: From mouse to human

An overview of the cardiovascular imaging program at UVA, with emphasis on the spectrum of imaging programs that span from pre-clinical imaging in small animals to clinical trials, with particular focus on PAD

Collaborators: Frederick Epstein, Craig Meyer, Brent French; industrial partnership: Siemens
Relevant local resources: Resources in Radiology and Cardiovascular Medicine, Molecular imaging core

Kenneth C. Bilchick – Imaging in Cardiac Electrophysiology

Explores the utility of MRI in cardiac electrophysiology, with examples of optimizing the selection of patients for cardiac resynchronization therapy.

Collaborators: Frederick Epstein, Jeffrey Holmes

Relevant local resources: Resources in Radiology and Cardiovascular Medicine, Molecular imaging core

Neuroimaging

Jason Druzgal –Neurological Imaging at UVA

An overview of the neurological imaging program at UVA, with emphasis on research infrastructure and thrust areas with the greatest potential for impact in the areas of cognitive disorders, traumatic brain injury and focused ultrasound.

Collaborators: Max Wintermark, James Stone, Jamie Morris, James Coan, Howard Goodkin, Donna Broshek

Relevant local resources: Resources in Radiology, Focused Ultrasound Center

Nicholas Tustison – Advanced neuroimaging at UVA, Imaging pipelines for neurodegenerative disorders, traumatic brain injury, movement disorders, epilepsy, stroke and brain tumors

An overview of the quantitative image analysis and computational processing capabilities for research involving imaging of small to large cohorts. Case studies involving various neuropathologies and normal development showcase some of the more prominent analysis tools currently in use at UVA and applicable to a spectrum of imaging-related research.

Collaborators: Max Wintermark, Jeff Elias, Mark Shaffrey, Jason Sheehan, James Stone

Relevant local resources: Resources in Radiology, UVA Cluster

Oncologic Imaging

Kimberly Kelly – Molecular Imaging of Cancer and Biomarker Discovery in Pancreatic Cancer

An overview of cancer imaging at UVA with an example of how a biomarker discovery project has shed new light on cancer biology and developed into a practical method for imaging pancreatic tumors in patients using nuclear imaging (PET & SPECT) of a targeted contrast agent.

Collaborators: Todd Bauer and Patrice Rehm

Relevant local resources: Buchanan Foundation, Molecular Imaging Core, UVA Cyclotron Facility

Concurrent sessions 2: 10:15 AM – 12:15 PM (Pavilions I, II, and III)

Session 2a (Pavilion I):

THE PATHOGENESIS OF ASTHMA: FROM EPIDEMIOLOGY TO THE SINGLE CELL

Overview: Thomas Platts-Mills (Chair) – The Rise in Asthma: Global Lessons in Disease Pathogenesis (Allergy)

Discuss:

- (1) the global impact of allergic disease;*
- (2) current views on reasons for the rise in asthma and other allergic diseases;*
- (3) current views on the role of environmental microbial exposure;*
- (4) the contribution of new and emerging allergens;*
- (5) challenges to understanding the link between allergens and allergic disease;*
- (6) Role of international collaborations in advancing knowledge;*
- (7) how genomics/proteomics and emerging technologies may impact our understanding of the disease.*

Research Talks

Peter Heymann – The Link Between Viral Infections and Asthma: Cause or Consequence?

- (1) Controversies regarding the role of viruses in asthma;*
- (2) Challenges to studying the role of viruses in childhood disease and in later life;*
- (3) Lessons from studies within the U.S. and abroad;*
- (4) Ongoing clinical trials involving experimental rhinovirus challenge;*
- (5) Partnerships with industry and interdisciplinary approaches.*

Gerald Teague – Challenges to Studying Severe Childhood Asthma

- (1) Insights into the pathogenesis of severe asthma in children from the NHLBI Severe Asthma Research Program;*
- (2) Use of hyperpolarized helium-3 MRI to image the asthmatic lung and future challenges to this approach;*
- (3) Applications and clinical challenges of image-guided specimen collection from the young asthmatic lung.*

Julia Wisniewski – Insights into Immunology of the Young Asthmatic Lung

- (1) Approaches to immunophenotyping the asthmatic lung.*
- (2) Describe the interdisciplinary research team and use of UVA Cores.*

**Session 2b (Pavilion II):
BRAIN, IMMUNOLOGY AND GLIA (BIG) – THE NEW FRONTIER IN TRANSLATIONAL
NEUROSCIENCE**

Speaker 1 and session organizer: Jonathan Kipnis – The role of the immune system in supporting brain function

Jonathan Kipnis is a Director of the newly established center for “Brain Immunology and Glia (BIG)” in the Department of Neuroscience at UVA. This field is interdisciplinary at its core, spanning the intersection of neuroscience and immunology. He will introduce this exploding field, discuss major recent breakthroughs, outline the challenges to be tackled, and the promise for translational advance in understanding and treating disorders of the nervous system. Examples from his own work and collaborations will be given.

Speaker 2: Alban Gaultier – Novel role for LRP1 during Experimental Autoimmune Encephalomyelitis (EAE)

Alban Gaultier is a new Assistant Professor of Neuroscience and a member of the BIG center. He works on mouse models of multiple sclerosis (EAE) and will discuss his recent insights into the mechanisms of clearance of myelin debris in the EAE brain. He has made innovative use of mass spectrometry to identify important molecules underlying the inflammatory response in EAE and to probe the roles that the innate immune system plays in the disease process. The strength of the UVA core mass spec facility will be discussed.

Speaker 3: Michael McConnell – Genetic mosaicism in human neurons

Michael McConnell is working on cutting edge research involving complex genomics, making use of human iPSCs (induced pluripotent stem cells). Even though his primary interest is in Neuroscience, his expertise is relevant to complex diseases more generally and his approaches will be of interest to a wide audience.

Speaker 4: Kevin Lee – Neuroinflammation as a therapeutic target for limiting cognitive decline after cardiopulmonary bypass surgery

Dr. Lee’s primary research interests are stroke and epilepsy and he has strong collaborative ties to clinicians and industry. He will discuss the role of neuroinflammation in cognitive decline after cardiopulmonary bypass surgery. This work is carried out in partnership with Irv Kron’s lab in the Department of Surgery.

**Session 2c (Pavilion III):
TRANSLATING MATHEMATICS INTO MEDICINE: SYSTEMS BIOLOGY AT UVA**

Jason Papin – Systems biology of metabolism: applications in microbial pathogenesis

Subject matter:

- 1) Provide overview of systems biology research at UVA and its relationship to other initiatives
- 2) Cover the application of modeling tools and high-throughput data integration for drug identification in infectious disease

Collaborations: Erik Hewlett; Infectious Diseases

Relevant local resources: Biomolecular Research Facility and Bioinformatics Core

Jeffrey Saucerman – High-throughput microscopy and modeling of cardiac myocyte hypertrophy

Subject matter: Use of computational modeling to describe signaling networks critical to the validation of drug targets.

Relevant local resources: Advanced Microscopy Facility, Keck Center for Live Cell Imaging

Peter Kasson – Systems biology, cloud computing and mechanisms of infectious disease

Subject matter: Use of large-scale computing to integrate structure, dynamics and microscopy for constructing utility models of drug resistance

Relevant local resources: Advanced Microscopy Facility, Keck Center for Live Cell Imaging, ITC

Kevin Janes – Cancer systems biology: small-scale approaches to big questions

Subject matter: Systems modeling of transcriptional networks underlying cell-to-cell heterogeneity

Collaborations: Kristen Atkins; Surgical Pathologist

Translational aspects: Patient stratification and response to targeted therapies

Concurrent sessions 3: 1:45 – 3:45 PM (Pavilions I, II, and III)

Session 3a (Pavilion I):

COLLABORATIONS LEADING TO INNOVATIONS: CARDIOVASCULAR RESEARCH AT UVA

Gary Owens

The AstraZeneca (AZ) alliance at UVA—how it formed and its current status and arrangement. The advantages and pitfalls of working with big pharma.

Gorav Ailawadi

Translational aspects of the AZ alliance, with focus on AAA and its impact in candidate drug selection.

Coleen McNamara

How the matured collaboration with Steve Rich, Center for Genomic Research, has aided the hunt for atherosclerotic gene targets in human populations.

Brant Isakson

How integration of multiple collaborations at UVA has provided novel concepts for blood pressure regulation

**Session 3b (Pavilion II):
NEW FRONTIERS AND OPPORTUNITIES FOR COLLABORATION IN NEURO-ONCOLOGY**

David Schiff: Malignant primary brain tumors, epitomized by the deadly glioblastoma, have been the beneficiaries of a tremendous increase in scientific understanding of their underpinnings but only modest therapeutic interventions. On the clinical front, our focus has been on therapeutic trials targeting angiogenesis, intracellular signaling, and immunotherapy. Advances in neuroimaging, particularly as relate to tumor metabolism, hold great promise in improving our understanding and management of these malignancies. Local delivery of therapies may allow us to circumvent the problem of the blood-brain barrier and take advantage of these tumors' lack of metastatic potential.

Roger Abounader: Receptor tyrosine kinases (RTKs) are co-deregulated in a majority of glioblastoma (GBM), the most common and deadly brain tumor. We show that RTKs c-Met, EGFR and PDGFR regulate microRNA-134 (miR-134) in GBM. We find that miR-134 is downregulated in human GBM and GBM stem cells and that it inhibits their proliferation, survival, self-renewal, stemness and xenograft growth. We identify KRAS and STAT5B as miR-134 targets. We thus establish miR-134 as a novel RTK-regulated tumor-suppressive hub mediating RTK and RTK-inhibitor effects on malignancy and stem cell pathobiology via KRAS and STAT5B. In addition to the above, our lab is working on identifying additional key regulatory microRNAs in glioblastoma. We plan to use them as therapeutic targets or agents. We are seeking collaborators with expertise in nucleic acid sequencing and bioinformatic analysis of RNAs and signaling pathways as well as experts in RNA/antisense delivery to the brain.

Richard Price: Critical challenges in treating brain cancers include overcoming radioresistance and targeting local therapies. Focused ultrasound provides one potential answer to both problems. The Price laboratory has shown that focused ultrasound has potential not only as a direct tumor-killing modality for brain tumors, but also as a means to target nanotherapies to the tumors. Microbubble-encapsulated nanotherapies can be released selectively within brain tumors via their rupture with ultrasound beams focused on the tumors, which also open up the vasculature to assist in tumor penetration. Potential collaborations could address optimal microbubble payloads, methods to address obstacles to focused ultrasound such as penetrating bone, and biophysical methods to enhance focusing of ultrasound beams.

Hui Zong: Cures for brain tumors will only be achieved when basic scientists and clinicians work together, using animal models and cell culture to probe deeply into mechanistic issues. I will present some of our recent work done with a mouse genetic mosaic model that reveals mutant/tumor cells at single-cell resolution *in vivo*. Using the model, we identified the glioma cell-of-origin in proneural subtype gliomas as the OPC rather than the NSC. This finding suggested a potential cellular target for therapy, but also demonstrated the importance of cell type-specific responses to oncogenic mutations for tumorigenesis. Finally I will discuss the great potential to use this mouse model to study tumor-niche interactions with living imaging methods, and to serve as a robust, quantitative pre-clinical glioma model to evaluate therapeutic effects of lead compounds for not only treatment but also prevention.

Panel Discussion: Panelists and organizer BJ Purow will discuss further the therapeutic challenges inherent in treating brain cancers such as glioblastoma, including delivery past the blood-brain barrier, need for precisely-targeted therapies within such a sensitive organ, relative radiation and chemotherapy resistance, cancer stem cells, and genetic heterogeneity. Opportunities for collaborations at UVA exist in areas such as local delivery, drug discovery, pharmacology, cell signaling, and neurodevelopmental biology.

Session 3c (Pavilion III):

UNDERSTANDING HUMAN BIOLOGY DURING INFECTION AND INFLAMMATION – and – LESSONS LEARNED ABOUT RESEARCH CAREERS FROM YOUNG AND SENIOR INVESTIGATORS

Summary: Each speaker will provide vignettes of science at the intersection of the human host with a microbe, with an eye towards anti-infective therapy targeted not at the microbe but at human pathways exploited by infection. In addition, the vignettes will be used to illustrate how to facilitate careers in science. This will include utilization of Cores, Centers, Training Programs, nontraditional funding mechanisms (including grants targeted to new investigators, seed funding, foundations, small business grants, intellectual property, DTRA, DIA), following where the science leads through hypothesis testing, science from the perspective of basic and clinical investigators, and finally pearls on laboratory management. We plan to call on the audience for your own thoughts on each of these topics!

Overview: William Petri (Chair). Health of impoverished infants in the developing world: infection, nutrition, cognitive development and vaccine failure.

Discuss: (1) Richness of longitudinal studies of human populations, with the tools improving every year for genomic, immunologic, nutritional and cognitive studies; (2) the neuroimmunology of motor and language development in infants; (3) why oral vaccines fail when they are most needed; and (4) the common ground of endocrinology, immunology and infectious diseases.

Research Talk 1: Molly Hughes. The role of chemokines in host defense against bacterial pathogens (immunology/ biodefense).

Discuss: (1) The role of chemokines in the host response to bacterial pathogens, especially in a time of emerging multi-drug resistance worldwide and fewer antibiotics to fight the war against the pathogens; (2) Work in Pakistan on bacterial pathogens (Aga Khan University); and (3) The role of partnerships with funding agencies (e.g., DoD, Gates Foundation) and collaborations within UVA and beyond.

Research Talk 2: Alison Criss. Comprehensive profiling of a host-pathogen interface: lessons learned from *Neisseria gonorrhoeae* interactions with the human immune system (Immunology/Bacterial Pathogenesis)

Discuss: (1) The cell biology, genetics, genomics, and biochemistry of how a pathogenic bacterium resists clearance by immune cells, with a goal of novel treatment options for an emerging “superbug”; (2) What happens when you let junior faculty loose: collaborations to study structure-function relationships in a variable family of bacterial membrane proteins (with L. Columbus, Dept. of Chemistry) and to investigate bacterial-immune interactions in primary human samples (with C. Warren and J. Eby, Div. of Infectious Diseases, Dept. of Medicine); (3) Pursuing (and sometimes attaining) funding earmarked for new investigators; and (4) Lessons learned about starting and growing a research laboratory.

Research Talk 3: Lukas Tamm. How structural biology may inform us about the outer membrane barrier to antibiotics in gram-negative bacteria and Ebola virus entry into mammalian cells.

*Discuss: (1) Defending bacteria from foreign intruders: Determination of the structures of two outer membrane proteins/pores from *Pseudomonas aeruginosa* by NMR. (2) Punching a hole with a fist: structure, function, and mutational studies of the Ebola virus fusion loop. (3) Teamwork is better than running circles in a silo: Establishing inter-departmental collaborations within UVA. (4) Looking beyond the horizon: International collaborations can really boost your research. (5) A case for research centers: UVA’s Center for Membrane Biology can help you!*

**University of Virginia School of Medicine
2013 Faculty Research Retreat
Lunch Roundtable Discussions**

Bag lunches will be provided in the Pavilion foyer. The [map of the Boar's Head](#) at the back of the program lists the locations listed below.

Regeneration and stem cells

Location: Pavilion 1
Barry Gumbiner

An opportunity for the UVA scientific community who are interested in this topic to discuss scientific opportunities. Because it is an initial meeting, no specific topics are preplanned, rather the interests of those attending should drive the direction of the discussion.

Genitourinary carcinogenesis

Location: Ednam Lobby
Helen Cathro, Stephen Culp

The goal of this session is to discuss the latest translational research dealing with all types of genitourinary cancers with a special emphasis on prostate, bladder, and kidney cancer. The target audience would be urologists, pathologists, radiation oncologists, and medical oncologists. The main focus is to discuss and define potential areas of collaboration dealing with translational research including the use of xenograft tumor models and tissue microarrays, biomarker studies, and ultimately clinical trials. The participant would develop a better understanding of the resources available for studying GU cancer at UVA, as well as potential areas for improvement using a multi-disciplinary approach.

How to enable basic science targets to bedside with efficient drug discovery infrastructure

Location: Blue Ridge Room
Michael Shim

How to initiate, foster, and proliferate opportunities present here at UVA to enable early scientific discovery to patentable therapeutics.

Glucose control: from intensive care to the ambulatory artificial pancreas

Location: Tack Room
Kenneth Brayman, Anthony McCall, Boris Kovatchev

In the hospital setting, the extent and magnitude of blood glucose fluctuations has been associated with mortality in a number of conditions, including but not limited to MI, stroke, and trauma. In diabetes, tight blood glucose control is the primary goal of any therapeutic intervention. Regardless of the setting, glucose control relies on monitoring and drug (primarily insulin) delivery technologies. In this session we review recent achievements in this field, ranging from in-clinic glucose control to ambulatory artificial pancreas suited for outpatient use in diabetes. Target audience: anyone in clinical, scientific, information technology or engineering disciplines who have to deal with these issues.

Virology at UVA

Location: Patio Room

Judy White

The goal of this session is to bring together virologists from multiple departments to discuss areas of mutual interest and potential collaborations.

Big data: challenges and opportunities for SOM-SEAS collaboration

Location: Pavilion 3

Kevin Skadron, Fred Epstein

"Big Data" poses massive challenges that span many disciplines. The sheer volume of data requires new computer engineering capabilities as well as new algorithms that can scale to massive data sets. Privacy and security are essential in managing many types of data. Many departments in SEAS have expertise that can help SOM faculty advance their data analysis capabilities, while SOM's needs will almost certainly pose interesting new research challenges for SEAS faculty. Both SOM and SEAS would benefit from a concerted effort to connect SEAS capabilities with SOM interests and vice versa, starting by highlighting the many already successful collaborations. To kick-start collaboration and boost Big Data capabilities, this session will focus on SOM-SEAS collaborations. The session will start with short presentations about existing collaborations related to Big Data, followed by a guided discussion of needs and opportunities for advancing SEAS-SOM collaborations in this area. In preparation for the retreat, additional documentation will be collected on current SOM-SEAS collaborations and individuals' areas of expertise in order to both create a passive directory and initiate an active collaboration connection mechanism."

Nanomedicine and drug delivery systems

Location: Arbor Room

Alexander Klibanov, John Hossack, Brent French

The purpose of this roundtable is to find possible synergies and collaborative potential for researchers interested in drug delivery approaches and applications.

Tumor microenvironment: inflammation, immune system, and metastasis

Location: Pavilion 2

Janet Cross, Amy Bouton, Vic Engelhard

The goal of this session is to identify new areas of scientific overlap among investigators studying host-mediated microenvironmental contributions to tumor progression and metastasis with a goal of fostering new collaborations.

Molecular imaging

Location: Hearth Room

Stuart Berr, Kimberly Kelly, Patrice Rehm

UVA is in the process of building a world-class molecular imaging program. Noninvasive molecular imaging provides a means by which to assess biological processes, which can be very useful for not only basic research studies but also clinically for detecting, diagnosing, and staging human disease. As imaging is useful for a wide variety of disciplines, we believe our center forms a nexus between disciplines including but not limited to the newly established UVA Centers of Excellence in Neuroscience, Cancer, and Cardiovascular disease. The round table discussion will be useful to those interested in (1) using molecular imaging to enhance translation research at UVA through the development of novel imaging radiotracers and testing them in first-in-human studies; (2) leveraging existing relationships and developing new relationships with pharmaceutical and biotechnology companies to pre-clinically and clinically test novel radiotracers; and (3) testing of new therapies using the results of established molecular imaging as an endpoint.

Data analysis and management challenges for comparative effectiveness and translational research at UVA

Location: Commonwealth Room

Ruth Bernheim, Jae Lee, George Stukenborg, James Harrison

Participants in this session will discuss biostatistical and data management challenges and issues when submitting research grant proposals. The target audience would be any interested clinical or basic science faculty.

Entrepreneurism and technology transfer at UVA: connections and partnerships

Location: Albemarle Room

Mark Crowell, Michael Straightiff

This session will discuss support at UVA for product development and technology transfer. Representatives of the UVA Licensing & Ventures Group and individuals with experience in the biotechnology sector will be present to discuss strategies and opportunities.

University of Virginia School of Medicine
2013 Faculty Research Retreat
Poster sessions (Pavilion – Board Room and Pre-function; Ednam Room)
Refer to the [plan of the Pavilion](#) for poster locations

Sessions to be held on Friday, 3:00 – 6:00 PM and Saturday, 4:00 – 6:00 PM

| Poster | Presenter, title, abstract | Room |
|---------------|---|--------------|
| Core 1 | Nicholas Sherman Mass Spectrometry Core Facility The Mass Spectrometry Core can provide services ranging from QA/QC to proteomics to quantification of a wide variety of molecules. We provide consultation, data analysis and assistance with papers and grants. | Pre-function |
| Core 2 | Stephen Turner University of Virginia Bioinformatics Core This poster features several of the services offered by the UVA Bioinformatics Core, and highlights several "research vignettes" of successful collaborations between the core and investigators in the School of Medicine. | Pre-function |
| Core 3 | Jan Redick Advanced Microscopy Facility Describes the capabilities of the Advanced Microscopy Core Facility at the School of Medicine. | Pre-function |
| Core 4 | Arthur Weltman Exercise Physiology Core Laboratory The Exercise Physiology Core Laboratory (EPCL) supports clinical research related to metabolic, cardiovascular and biochemical responses to exercise. In addition, the EPCL provides expertise in measures of body composition and regional distribution of body fat, physical function, resting metabolism and imaging. The EPCL serves both research and community users. | Pre-function |
| Core 5 | Wenhao Xu Build a Better Mouse The goal of the Gene Targeting and Transgenic Facility (GTTF) is to utilize advanced transgenic and gene targeting technologies to efficiently produce and preserve genetically engineered mice for animal model research for investigators at UVA. In order to achieve this goal, GTTF outlines the following strategic plan: build a team of staff with expertise in creating animal models; streamline processes and improve efficiencies; enhance the use and application of ES cell based technology; offer customized model design, development and preservation; and support research grant applications and faculty recruitments. | Pre-function |
| Core 6 | Stuart S. Berr UVa Molecular Imaging Core Laboratory The UVa Molecular Imaging Core Laboratory (UVaMIC) provides high resolution radiology with equipment optimized for rodent imaging. The core houses state of the art imaging equipment geared towards noninvasive anatomical and functional imaging of rats and mice. Much of the equipment was purchased with funds from the NIH. It includes a state of the art 7.0 Tesla ClinScan (Bruker/Siemens) MRI, a 4.7 Tesla Varian MRI, a micro CT-SPECT scanner developed in-house by Professor Mark B. Williams, a fluorescence/bioluminescence IVIS Spectrum (Perkin Elmer) scanner, and a micro positron emission tomography (PET) Focus 120 (Siemens) scanner. This poster highlights the capabilities of the instrumentation along with example images acquired from investigators at UVA. | Pre-function |
| Core 7 | Stuart S. Berr UVa Molecular Imaging Radiochemistry Core Laboratory We recently installed a cyclotron that was purchased with funds from an NIH High-End Instrumentation grant. As part of the purchase, we forged a partnership with PETNET Solutions Inc. (Siemens Medical Solutions USA) in which they staff and | Pre-function |

| Poster | Presenter, title, abstract | Room |
|---------|---|--------------|
| | <p>maintain the cyclotron lab in exchange for being able to operate a commercial radiopharmacy onsite. The cyclotron produces radioisotopes (e.g., [18F]fluorine, [11C]Carbon and [13N]Nitrogen) which can be chemically bound to molecules that target specific biological processes. The resulting radioactive probes can be imaged using positron emission tomography (PET). The probes can be used as a research tool in animals and humans and can be used to assist in the clinical management of patients. This poster will provide an overview of the capabilities of our radiochemistry lab and the probes we and PETNET are currently making.</p> | |
| Core 8 | <p>Jeffrey Ellena Biological Nuclear Magnetic Resonance Spectroscopy Core The content and capabilities of the BioNMR Spectroscopy Core will be described and several recent publications containing work which utilized the Core will be cited.</p> | Pre-function |
| Core 9 | <p>Joanne Lannigan Flow Cytometry Core Facility Services The Flow Cytometry Core Facility provides all investigators at the University of Virginia access to high quality, cost effective flow cytometry services. In addition to providing access to a variety of instrumentation, the FCCF also provides scientific expertise necessary to effectively use this technology to enhance the scope and quality of scientific research performed at the University. The state of the art facility occupies approximately 1800 sq. ft. and houses a variety from basic to high end flow cytometry instrumentation. This includes a three laser 8 color FACSVantage SE TurboSort DIVA, a six laser 18 color Reflection Cell Sorters, both which provide 4-way high-speed cell sorting and complex analytical services. In addition, the facility has two 2-laser 4-color FACSCalibur benchtop analyzers as well as a 3-laser 5-color and a 4-laser 10-color analyzers. Other instruments available include a three laser 9-color CyAn ADP LX benchtop cytometer, a four laser LSRFortessa with 16 fluorescent detectors, an ImageStreamX imaging flow cytometer and a Luminex 100 IS bead-based multiplex analyzer. For those requiring flow cytometry access in a BSL-3 environment, the FCCF has expanded services to the BSL3 suite in MR6 with a five laser 17 color high speed Influx cell sorter. A multi-TB server is available for data storage as well as site licenses for data analysis software. Researchers have the option, once trained, of performing their own analysis or utilizing the expertise of the facility's staff to run their samples for them. Specialized training classes are offered for those researchers who wish to better understand the principles and techniques employed in this technology and prefer to directly acquire and/or analyze their own samples.</p> | Pre-function |
| Core 10 | <p>Yongde Bao Analytical tools offered in DNA Sciences Core to facilitate basic or clinical research The DNA Sciences Core has developed and optimized a variety of analytical tools to facilitate the nucleic acid related basic and clinical research in the Medical School. These include deep DNA sequencing in different platforms, which have seen unprecedented embrace by the research community and thereby creating a great impact in the field of genetic and genomic research. Among the tools in the display are microarray analysis, real time PCR, and other research tools, which altogether afford a broad coverage in the multi-discipline study of structural biology, gene expression and regulation, and the analyses of disease related copy number changes and mutations.</p> | Pre-function |
| Core 11 | <p>Patcharin Pramoonjago The Biorepository and Tissue Research Facility (BTRF) The Biorepository and Tissue Research Facility (BTRF) is the main core facility at UVA supporting procurement, processing, banking, and analysis of human biospecimens. The services provided by the BTRF fall into two general categories, biorepository activities and tissue analysis, and many of these services can be vertically integrated with each other to allow for 'one-stop shopping.'</p> | Pre-function |

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| | <p>The biorepository activities of the core include procurement and processing of human biospecimens for specific studies, as well as maintaining a tissue bank. BTRF technicians are on hand to obtain tissue specimens from Surgery, Pathology and other clinical areas of the UVA Hospital. Tissues may be fixed, snap frozen or dissociated for cell lines or xenograft implantation. There are currently approximately 14,500 banked frozen tissue specimens and 16,500 banked paraffin blocks available in the biorepository, with an accrual rate of 2000 new specimens of each preservation type per year. The BTRF is also an official access point for researchers to the Pathology Department clinical archives, consisting of paraffin blocks and slides collected over a period of many decades. The BTRF is able to fractionate and preserve biofluids, such as blood, urine, sputum, and ascites collected by study personnel. Specialized processing such as purification and cryopreservation of lymphocytes from peripheral blood is also available. The BTRF supports tissue-based analytic techniques. Basic histology-services for human tissue samples include formalin fixation and processing of tissue into paraffin blocks (FFPE), sectioning of FFPE and frozen tissue, and basic hematoxylin and eosin (H&E) staining. Advanced histology-services include automated immunohistochemistry, special histologic stains, histology-guided macrodissection, tissue microarray construction, laser microdissection, photomicroscopy and virtual microscopy. Molecular fractionation and characterization-services include robotic isolation of DNA, RNA and protein from histologically-defined, frozen or fixed tissue specimens, with nucleic acid quality and quantity assessment.</p> <p>Our services make possible new insights into disease mechanisms by the analysis of tissues and biofluids, assist in the discovery and validation of new clinical biomarkers, and support clinical trials of novel diagnostic tests and therapies.</p> | |
| Core 12 | <p>John Shannon Shared Instrumentation Core</p> <p>The Shared Instrumentation Core provides access at all hours to user operated circular dichroism, fluorescent plate reader, absorbance plate reader, microscope slide scanner, densitometer and real time cell analysis instruments with reservations through Collab. HPLC, fluorescent gel scanning and slide scanning are available as core operated services. All instruments and services are located in Jordan Hall.</p> | Pre-function |
| Core 13 | <p>Lori Elder Clinical Research Unit</p> <p>In order to bring discoveries to patients, there must be a location where clinical research studies can take place with skilled staff to ensure high quality safe research practices. The Clinical Research Unit (CRU) of the School of Medicine Clinical Trials Office provides these services/facilities for investigators conducting inpatient and outpatient clinical and translational research at the University of Virginia. The services provided by the CRU staff have replaced the nursing services formerly provided by the General Clinical Research Center (GCRC) which recently closed when the NIH GCRC grant program ended. The CRU services include clinical research facilities (supporting both outpatient and inpatient studies) and research support services.</p> | Pre-function |
| Core 14 | <p>Thomas M. Guterbock A Productive Partnership: UVA's Center for Survey Research and the Department of Public Health Sciences</p> <p>Since its inception, the UVA Department of Public Health Sciences has developed a strong teaching and research relationship with the Center for Survey Research [CSR]. Projects have included among others: Anthem/TEACH, Human Genetics and EMR Focus Groups, HPV Vaccine Uptake studies, the Jefferson Area Community Survey, and Family Health History recruitment. We propose to highlight these projects and to introduce our services to faculty in attendance. CSR has a long history of health-care related project work. Previous clients have included: The Cancer Center, Institute for Practical Ethics, UVA Physicians Group,</p> | Pre-function |

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| | <p>Department of Anesthesiology, The Heart Center, Department of Family Medicine, Virginia Department of Public Health, American Medical Student Association, and Virginia Institute of Autism, among many others.</p> <p>CSR is a full-service research facility at the University of Virginia, a unit of the Weldon Cooper Center for Public Service. Established in 1988, CSR has completed hundreds of scientific surveys. In all aspects of our work, our mission is to help our clients to achieve their goals by providing survey-based information that is objective, accurate, relevant, timely and clear. •</p> <p>Our clients have included federal agencies, state and local governments, and many University of Virginia academic departments, as well as School of Medicine faculty and students. We provide assistance with all phases of survey work: design, sampling, questionnaire development, pretesting, data collection, and analysis and reporting. CSR operates a computer-assisted telephone interviewing laboratory and also offers surveys via the Internet, postal surveys, focus groups and semi-structured interviewing services.</p> <p>For School of Medicine faculty, collaboration with CSR offers benefits:</p> <ul style="list-style-type: none"> • Effective and affordable study design • Competitive grant proposals • Pre-testing, focus groups, pilot tests • Complex survey design and capability in telephone, web-based, and multi-mode designs • Highest possible rates of response • Measured reliability and validity • A ready-to-use data file for you to analyze OR • Analysis to your specifications • Full report options | |
| Core 15 | <p>Ammasi Periasamy The W.M. Keck Center for Cellular Imaging – A University Imaging Center The poster will focus on the advanced imaging systems and the service available at the Keck Center for Cellular Imaging (KCCI) located at the Physical and Life Sciences Building (PLSB, B041). The topics presented to the participants will include: the broad range of state-of-the-art molecular imaging technologies including wide-field, confocal, multiphoton, intravital imaging, TIRF, FRET, FLIM, FRAP, photo-ablation and others; KCCI as a resource for training, teaching and consultancy in matters of light microscopy; and KCCI and its involvement in innovative research methodologies and development of new imaging approaches and related technologies in cooperation with UVA faculty.</p> | Pre-function |
| Core 16 | <p>Marya Dunlap-Brown Molecular Assessments & Preclinical Studies Core Research Facility The Molecular Assessments and Preclinical Studies (MAPS) Core is a cost-effective preclinical research facility dedicated to investigations of human disease models in rodents and relevant therapeutic drug development systems. Although the Core's roots are in cancer investigations, over the years we have expanded services to include investigations into a wide range of disease models. The MAPS Core is centrally located on the first floor of Jordan Hall in Room 1221 and is available to all University of Virginia investigators. Our services move research projects from the bench or from a patient sample into an in vivo rodent model context, thereby enhancing the translation of UVA investigator discoveries into useful knowledge for clinical therapeutic applications in the effective management of human diseases. The MAPS Core services are an integral part of the UVA translational and innovation research initiatives.</p> | Pre-function |
| Core 17 | <p>Linda Langman The cGMP Human Tissue and Cell Processing Facility at The University of Virginia The University of Virginia cGMP Human Cell Processing Facility is a specialized</p> | Pre-function |

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| | <p>laboratory completed in 2004 at the Aurbach MR Building at Fontaine Research Park. Funds from the School of Medicine were efficiently used to build and equip the facility while operations and research have been paid for with generous donations from Paul and Diane Manning. The facility has permitted development of human pancreatic islet cell isolations for clinical, autologous and allogeneic transplantation, the only program of its kind in the state of Virginia, Maryland, West Virginia and North Carolina. Along with performing 16 autologous human islet transplants, the facility also supplies human islets to investigators and research laboratories inside and outside of UVA. The facility maintains rigorous quality assurance programs consistent with FDA qualification and as such, is uniquely positioned to offer valuable services to the University's research community by providing cell isolation, clean room services, program development, and cGMP training toward IND data collection. The mission of the cGMP Human Cell Processing Facility core is to advance clinical therapy programs at the University of Virginia by permitting researchers across the University access to a State of the art, FDA qualified facility that can provide the qualified space to advance basic science research toward clinical trials. The mission of the core includes becoming financially sustainable by offering an important resource to University researchers that is unavailable at most other institutions.</p> <p>A look inside and a blueprint of the facility is included.</p> | |
| Core 18 | <p>Gretchen N. Arnold The BioConnector: Getting Researchers Connected to the Tools, Experts and Resources They Need The University of Virginia's Health Sciences Library, Bioinformatics Core, and Division of Biomedical Informatics formed a partnership to provide coordinated research informatics support services for the School of Medicine. The BioConnector is a physical and virtual space where researchers receive concierge-type support connecting them quickly to the tools and resources they need for managing and analyzing research data. Services include access to a suite of informatics tools, de-identified clinical data, data management planning expertise, metadata services, and a physical space designed to support collaboration among researchers. The BioConnector will continue to evolve providing informatics tools and services for the School of Medicine based on the needs of the research community</p> | |
| 1 | <p>Kenneth Tung The unique properties of neonatal NK cells predispose newborns to autoimmune ovarian disease (nAOD) induced by maternal autoantibody The transfer of maternal autoantibody (autoAb) to the progeny can cause neonatal autoimmune diseases. An example is the fatal congenital heart block elicited by maternal SSA/SSB antibodies in Sjogren's patients. Disease mechanism is unknown but can now be investigated in a nAOD model developed in our laboratory. Ovarian inflammation and atrophy occurs in C57BL/6 Rag KO pups after the exposure to maternal autoAb against ovarian zona pellucida 3 within 1-5 days of life. Resistance to nAOD induction in NK cell-depleted Rag KO pups, and NK cell deficient (Rag/common gamma chain [Rag/gc] double KO) mice demonstrates the critical role of NK cells. Notably, neonatal but not adult NK cells restore nAOD in Rag/gc KO pups. Compared to adult NK cells, neonatal NK cells have lower expression of Ly49 receptors and higher frequency of the CD27+ subset. We now show that the expression of CD27, CXCR3 and IFNγ by neonatal NK cells are crucial for nAOD. Furthermore, Ly49C/I-depleted adult NK cells acquire the ability to induce nAOD. This suggests that the low expression of Ly49 reduces the activation threshold and enhances the pathogenic capacity of neonatal NK cells. Lastly, FcγRIII expression on both neonatal NK cells and ovarian resident macrophages and dendritic cells (APC) is obligatory for nAOD induction. However, ovarian APC requirement is not ontogenetically regulated. We conclude that the unique properties of neonatal NK cell predispose newborns to autoimmune disease by maternal autoAb.</p> | Board |

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| 2 (Fri.) | <p>Gordon Laurie Targeting of Heparanase-Modified Syndecan-1 by Prosecretory Mitogen Lacritin Requires Conserved Core'GAGAL' and Sulfated Glycosaminoglycans Likely as Stubs</p> <p>Cell surface heparan sulfate (HS) proteoglycans shape organogenesis and homeostasis by capture and release of morphogens through mechanisms largely thought to exclude the core protein domain. Yet, heparanase deglycanation of the N-terminal HS-rich domain of syndecan-1 (SDC1), but not SDC2 or -4, is a prerequisite for binding of the prosecretory mitogen lacritin (Ma, P, Beck SL, Raab RW et al, Journal of Cell Biology 174:1097-1106, 2006). We now report that ligation by lacritin is centered on the conserved and hydrophobic core sequence 'GAGAL' in SDC1, and seemingly on the heparanase shortened HS chains of ~4 - 5 kD with which it is nestled. Swapping out GAGAL for SDC2's 'GADED', or for SDC4's 'GDLDD' - both less hydrophobic - abrogates binding. Removal of all predicted HS chains by triple point mutation, or with competitive inhibitor xyloside, or suppression of sulfation in the presence of chlorate, also diminish or erase binding. Bridging hydrophobic GAGAL and anionic HS chain stubs is lacritin's C-terminal amphipathic alpha-helix. Triple point mutation of lacritin's hydrophobic face Leu108/Leu109/Phe112 and double or single point mutation of hydrophilic (and largely cationic) face Glu103/Lys107 or Lys111 eliminates binding. Carving a hybrid hydrophobic/electrostatic docking site out of SDC1 in a manner dependent on endogenous heparanase is a dynamic process appropriate for subtle or broad epithelial regulation in morphogenesis, health and disease. Specificity from joint core/HS binding may be common to other growth factors including Wnt, BMP, midkine and pleiotropin that share affinity for both elements.</p> | Board |
| 2 (Sat.) | <p>Gordon Laurie Tear Lacritin Rescues Dry Eye Stressed Epithelia Via a Rapid Autophagic Pulse That Restores Metabolism</p> <p>Survival of the eye surface is not clearly understood. This differs from skin where cornification plays a dominant role. Tears cover the surface of the eye, and are deficient in dry eye, the most common eye disease affecting at least 5% of the world's population. Only a tiny fraction of the tear proteome is selectively downregulated, including lacritin, an eye-selective mitogen that promotes basal tearing when topically applied to rabbit eyes. Here we discover that survival is entirely tear lacritin dependent, and elucidate the mechanism as a transient and rapid (within 1 min) acceleration of autophagic flux to promptly restore cellular metabolism and mitochondrial fusion - in keeping with lacritin's short residence time on the eye before drainage into the nasolacrimal duct. Accelerated flux appears to derive from lacritin stimulated acetylation of FOXO3 as a novel ligand for ATG101 and coupling of stress acetylated FOXO1 with ATG7 (that remains uncoupled without lacritin), and is sufficient to selectively divert huntingtin mutant Htt103Q aggregates largely without affecting non-aggregated Htt25Q. This is in keeping with stress as a prerequisite for lacritin stimulated autophagy. Lacritin targets the ocular cell surface proteoglycan syndecan-1 via its C-terminal amino acids L108/L109/F112. Thus lacritin confers corneal cytoprotective activity to tears, presumably in a pulsatile manner as tears are replenished.</p> | Board |
| 3 | <p>Gordon Laurie Tissue Transglutaminase is a Negative Regulator of Monomeric Lacritin</p> <p>BioactivityMolar accounting of bioactive fluids is rarely considered despite a growing proteomic focus in epithelial biology. Essential for the viability of the surface epithelium of the eye and for normal vision is the thin, but proteomically rich, tear film in which the small tear glycoprotein lacritin appears to play a prominent prosecretory, cytoprotective and mitogenic role. Although optimal molar levels in cell culture are 1 - 10 nM over a biphasic dose optimum, ELISA suggests a sustained tear lacritin concentration in the low micromolar range. Here we unexpectedly discover that tissue transglutaminase (TGM2) in tears appears to negatively regulate levels of epithelially bioactive lacritin. Blotting for lacritin in</p> | Board |

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| | <p>human tears or homogenates of lacrimal and salivary gland surprisingly detected immunoreactive 60 to 83 kDa material with a prominence that substantially exceeded the expected 18 - 23 kDa band. Exogenous TGM2 initiates lacritin crosslinking within 1 min and is complete by 90 min - even with as little as 0.1 nM lacritin. Crosslinking is absent when TGM2 is inactive or EDTA chelated. Utilized is the acceptor glutamine125 in the syndecan-1 binding domain, and donors lysine101 and 104. Cross-linked lacritin, unlike 18 kDa monomer, binds syndecan-1 poorly. Since syndecan-1 binding is necessary for lacritin mitogenic and cytoprotective activities, cross-linking negatively regulates lacritin bioactivity.</p> | |
| 4 | <p>Ian J. Glomski <i>In vivo</i> bottlenecks occur in both portals of entry of inhalational <i>B. anthracis</i> infections <i>Bacillus anthracis</i> causes anthrax and is highly lethal when inhaled. Mouse inhalational infections can initiate in either the upper or lower respiratory system. In the upper respiratory system, bacteria colonize and disseminate from the nasal associated lymphoid tissue (NALT), whereas in the lower respiratory system <i>B. anthracis</i> either disseminates after being transported to the lymph nodes by phagocytes acting as a Trojan horse or by direct growth and dissemination from the alveolar sacs of the lung. Previous research found the intranasal 50% lethal dose (LD50) in Balb/cJ mice is 3 log₁₀ higher than for subcutaneous infections. This suggests that only a small proportion of the inoculum is necessary to cause disseminated inhalational anthrax and that <i>B. anthracis</i> must pass through an <i>in vivo</i> bottleneck before dissemination. Yet, lung-based infections showed tissue damage at early time points, which may enable <i>B. anthracis</i> to circumvent the bottleneck. We hypothesize that bacteria pass through a bottleneck in upper respiratory infections, resulting in a subset growing within the NALT; however, the bacterial population can circumvent the bottleneck by growing en masse within the lumen of the lung. We also sought to compare the dissemination patterns of these infections by exploiting these predicted bottlenecks. Clonal analysis was used to determine the site and size of bottlenecks. Mice were infected intranasally with 106 to 108 spores of an equally proportioned mix of 5 luminescent clones differentiated by unique recombinant DNA tags. The infections progressed until light was found in the kidney, signifying a systemic infection. Harvested clones from the NALT, NALT-draining cervical LNs (cLN), lungs, mediastinal LNs (mLN), and kidneys had their CFU burden enumerated and clonal identity established by PCR. The kidneys were chosen as a proxy for the disseminated infection due to high CFU burden. Clonal proportions were used to determine the effective population size, an estimate of bottleneck size. Clonal proportions were reduced for both NALT and lung-based infections as bacteria passed through bottlenecks. NALT-based infections had all clones germinate in the NALT and passed through a bottleneck as the clones reached the cLN. Clones in the cLN eventually disseminated into the bloodstream and colonized the kidneys. Similarly, lung-based infections also passed through a bottleneck, as they had matching clones in their kidney and lungs. The effective population size for NALT-based infections was 0.72 and 1.65 for lung-based infections.</p> | Board |
| 5 | <p>Shayn Peirce-Cottler Use of Oxygen-Sensitive Luminescent PLA Nanoparticles in the Design of a Wound Diagnostic Device <u>Introduction:</u> The annual incidence of chronic wounds including pressure, venous and diabetic ulcers is estimated to be six million patients and the estimated costs for managing and treating these wounds in the United States is expected to exceed \$20 billion per year. Currently, there are no methods for early detection of these wounds and can take up to four months to determine if a wound is healing or on the path of becoming a chronic wound. The most widely used metric to assess wound healing is wound size; however, shrinkage in wound size only loosely correlates with actual wound healing. The inability to determine whether or not significant pathology exists makes assessing wound healing prone to inaccuracies, which can</p> | Board |

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| | <p>lead to poor clinical decisions and less desirable outcomes. The oxygen level within a wound bed is directly related to the extent of pathology and its potential to heal. Currently, measuring of oxygen levels within wound beds to determine prognosis is severely limited mainly stemming from the fact that current techniques are expensive, inaccurate and provide only indirect, point measurements of oxygenation levels. This project aims to develop an inexpensive, quantitative diagnostic tool capable of detecting oxygenation levels across the entire wound bed. This diagnostic tool encompasses two components: Component 1 - a nanoparticle-based oxygen sensor that is delivered topically into the wound bed and Component 2 - a light source that activates the dual-emissive property of the nanoparticles coupled to a handheld digital camera that captures the colorimetric readout of the illuminated nanoparticles and by a ratiometric method can indicate oxygen levels in the wound bed.</p> <p>Materials and Methods: Using solvent-free lactide polymerization, we formulated a novel, dual-emissive luminescent dye (iodide-substituted difluoroboron dibenzoylmethane, BF₂dbm(I)) conjugated to poly(lactic acid) (PLA), a biocompatible and biodegradable polymer, into nanoparticles, creating oxygen-sensing boron nanoparticles termed “BNPs”. BNPs enable ratiometric oxygenation sensing by giving a colorimetric readout of oxygen levels; “blue” fluorescence (F) serves as a standard, and the “green/yellow” phosphorescence (P) signal increases as O₂ levels decrease (Figure 1A.) Component 2 consisted of a custom designed ring light attachment (20 LEDs that illuminate at a 380 nm wavelength) to a standard digital SLR camera. Component 2 takes advantage of the intrinsic sensitivity of the three color channels of a color camera as a function of wavelength to quantify the fluorescence and phosphorescence signals and P/F ratio emitted from the BNPs via a MATLAB program.</p> <p>Results and Discussion: We demonstrated the ability to successfully fabricate BNPs from BF₂dbm(I)PLA, and a sterilization study confirmed that filtering of BNPs with a 0.2 μm filter effectively sterilizes the BNPs, while still preserving the biomaterial’s luminescent and morphological properties. The observed radius of the filtered BNPs decreased slightly from 41.1 nm to 39.25 nm, the polydispersity index decreased slightly from 0.301 to 0.243, and the luminescent properties (fluorescent/phosphorescent peaks) of the filtered BNPs remained unchanged as compared to unfiltered BNPs. Sterilized BNPs (1 mg/mL) were applied topically to 1-cm diameter full thickness wounds on the mouse dorsum (Figure 1B). On days 4, 7 and 9 post wounding, the wound bed was imaged (Figure 1B,C) using the specially designed hand-held camera. The MATLAB program was used to process the images of excited BNPs, and successfully differentiated oxygenation levels across the wound bed. Moreover, wound healing time was not significantly different between control and treatment groups, confirming the biocompatibility of the BNPs.</p>  <p>Figure 1. A) Optical properties of BNPs under UV excitation in ambient air environment and an O₂-purged environment. B,C) Images of UV-excited wound beds with BNPs (B) and without BNPs (C) at day 4.</p> <p>Conclusions: We present the first steps toward the development of a wound diagnostic device capable of spatial mapping of oxygenation levels within a wound bed. Future work will be conducted to optimize BNP uptake in the wound bed to increase overall BNP uptake and decrease BNP uptake time. Further, oxygenation calibration of the device will be conducted against a commonly used oxygen probe to ensure accurate oxygenation readouts from the device.</p> | |
| 6 | <p>James H. Moak A Clinical Decision Rule for Thoracic and Lumbar Spine Fractures: Does the NEXUS rule work below the neck?</p> | Board |

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| | <p>Background. The National Emergency X-Radiography Utilization Study (NEXUS) rule, which screens for potential cervical (C-) spine injury, suggests that imaging is not warranted in patients with no midline tenderness, no focal neurologic deficit, normal alertness, no intoxication, and no distracting injury. This rule has a reported sensitivity of 91-100% and specificity of 13-37% for clinically significant injuries.</p> <p>Objectives. No prior studies have examined whether a variation of this rule might be useful for detecting thoracic (T-) and lumbar (L-) spine injuries. We sought to determine the value of a clinical decision rule based on NEXUS for detecting any injury, and any clinically significant injury, to the T- or L-spine. The modified rule substitutes midline T- or L-spine tenderness in place of C-spine tenderness.</p> <p>Methods. This prospective observational study was conducted over a 12-month period at a state Level 1 academic trauma center with an ED census of 60,000/year. The study involved a convenience sample of ED patients > 17 years evaluated by the trauma team. Data sheets were completed by Emergency Medicine attending physicians after initial patient evaluation and stabilization. Patients were excluded if they did not survive >10 minutes, sustained only penetrating trauma, had T- or L-spine cross sectional imaging prior to arrival, or were not ultimately evaluated by the trauma service. Intoxication and distracting injury were determined subjectively by the treating attending without specific parameters. A significant T- or L-spine injury was defined a priori as one requiring surgical intervention or treatment with a rigid brace. A standardized data abstraction form was used for review of hospital records. The test characteristics of the modified NEXUS rule were determined for any injury and for any clinically significant injury. Data was analyzed using descriptive statistics and proportions with confidence intervals.</p> <p>Results. Data sheets were collected on 458 patients, among whom 98 were excluded because they did not survive >10 minutes (12), sustained only penetrating trauma (35), had imaging completed prior to arrival (39), or were not evaluated by the trauma team (12). The study population thus consisted of 360 patients. The average age was 44.7 years, and 244 (68%) were male. The test characteristics of the modified NEXUS rule for detecting any T- or L-spine injury were sensitivity 94.0% (95%CI 84.7-98.1), specificity 14.0% (95%CI 10.3-18.6%), positive predictive value (PPV) 20.0% (95%CI 15.8-24.9%), and negative predictive value (NPV) 91.1% (95%CI 77.9-97.1%). The performance of the rule for detecting a clinically significant injury was sensitivity 92.3% (95%CI 73.4-98.7), specificity 12.9% (95%CI 9.6-17.1%), PPV 7.6% (95%CI 5.0-11.3%), and NPV 95.6% (95%CI 83.6-99.2%). Two patients (0.6%) with clinically significant injuries were not identified by the rule. One was a 66-year-old male with ankylosing spondylitis who fell from a lawn mower and sustained multiple C-spine fractures as well as T7 and T8 fractures that were managed surgically. The other was a 65-year-old male motorcyclist with T10 and L5 fractures treated with a rigid brace.</p> <p>Conclusion. When modified for T- and L-spine tenderness, the NEXUS rule has very good sensitivity (>90%) for identifying spinal injuries below the neck. Caution may be warranted when applying this rule in older patients.</p> | |
| 7 | <p>Bijoy K. Kundu Quantitative PET Imaging Detects Early Metabolic Remodeling in a Mouse Model of Pressure Overload Left Ventricular Hypertrophy <i>in vivo</i> Introduction: We proposed that metabolic remodeling in the form of increased myocardial glucose analogue 2-[18F] fluoro-2deoxy-D-glucose (FDG) uptake precedes and triggers the onset of severe contractile dysfunction in pressure overload left ventricular hypertrophy (LVH) <i>in vivo</i>. To test this hypothesis we used a mouse model of transverse aortic constriction (TAC) together with Positron Emission Tomography (PET) and assessed serial changes in cardiac metabolism and function over 7 days. Methods: PET scans of 16 C57BL/6 male mice were performed using a microPET Focus F-120 scanner under sevoflurane anesthesia. A 10-minute transmission scan was followed by a 60-minute dynamic FDG-PET scan with cardiac and</p> | Board |

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| | <p>respiratory gating. Blood glucose levels were measured before and after the emission scan. Transverse aortic constriction (TAC) and sham surgeries were performed after baseline imaging. Osmotic mini-pumps containing either propranolol (5 mg/kg/day) or vehicle alone were implanted subcutaneously at the end of surgery. Subsequent scans were taken at days 1 and 7 after surgery. A compartment model, in which the blood input function with spill-over and partial volume corrections and the metabolic rate constants in a 3-compartment model are simultaneously estimated, was used to determine the net myocardial FDG influx constant, Ki. The rate of myocardial glucose use, rMGU, was also computed. Estimations of the ejection fractions (EF) were based on the high resolution gated PET images.</p> <p><u>Results:</u> Mice undergoing TAC surgery exhibited an increase in the Ki (580%) and glucose usage the day after surgery indicating early adaptive response. On day 7 the EF had decreased by 24% indicating a maladaptive response. Average Ki increases were not linearly associated with increases in rMGU. Ki exceeded rMGU by 29% in the TAC mice. TAC Mice treated with propranolol attenuated rate of FDG uptake, diminished mismatch between Ki and rMGU (9%) and rescued cardiac function.</p> <p><u>Conclusions:</u> Metabolic remodeling precedes and possibly triggers the onset of severe contractile dysfunction. Both are prevented by treatment with propranolol. Early detection of metabolic remodeling may offer a metabolic target for modulation of hypertrophy.</p> | |
| 8 | <p>Brent A. French Comparison of Displacement-Based and Radial Uniformity Ratio Estimate Dyssynchrony Metrics in Serial Echocardiography of Post-Infarct Mice</p> <p><u>Background:</u> Many of the existing dyssynchrony metrics rely on myocardial strain measurements, including circumferential uniformity ratio estimate (CURE) and related metrics such as RURE. Since strain is a derivative of displacement, amplification of noise in strain calculations due to noisy displacement data is common, thus compromising strain-based dyssynchrony metrics. We propose a novel displacement-based dyssynchrony metric, called Dyskinesia Index (DI), that is sensitive and consistent in detecting left ventricular (LV) dyssynchrony, particularly dyskinesia.</p> <p><u>Methods:</u> Long-axis (LA) cines of 7 C57BL/6 mice were captured with a 30MHz ultrasound transducer. Baseline (B) data were acquired prior to myocardial infarction (MI) induced by a 1-hr occlusion of the LAD followed by reperfusion. Thereafter, cines were acquired at 2, 4, 7, 14 and 28 days post-MI. Displacements were quantified using speckle tracking on the LA cines. DI was determined using Fourier analysis of radial displacement distributed along the endocardial wall, and is the square root of the ratio of the zero-order power term to the sum of zero-order and a scaled first order power terms.</p> <p><u>Results:</u> DI was compared to RURE at Baseline (B) and at 5 time-points post-MI. DI values at B are consistently close to 1 (0.96 ± 0.01), and decrease significantly early after MI due to dyskinesia, reaching a minimum at D4 (0.64 ± 0.08). After the first week, motion in the infarct zone becomes more akinetic due to scar formation and DI values partially recover to a plateau late after MI. ANOVA reveals significant differences between B and all post-MI time-points ($p < 0.05$). In contrast, RURE is less sensitive to dyskinesia at D4 and post-MI estimates are only significant from B for after D4 ($p < 0.05$).</p> <p><u>Conclusion:</u> Strain-based measures of dyssynchrony are error-susceptible without adequate filtering of displacement data. DI has been shown to work well in ultrasound B-mode images, where image artifacts can degrade displacement data.</p> | Board |
| 9 | <p>Brent A. French Natural Killer T cells Play a More Critical Role in Reperfusion Injury Than in the Hyperglycemic Exacerbation of Infarct Size</p> <p><u>Introduction:</u> Invariant Natural Killer T (iNKT) cells express a T cell receptor encoded by the Jalpha18 gene that recognizes glycolipid antigens presented by</p> | Board |

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| | <p>CD1d. These same iNKT cells have recently been implicated in the hyperglycemic exacerbation of lung ischemia/reperfusion injury. Thus, we hypothesized that Jalpha18^{-/-} mice, which lack iNKT cells, would similarly be protected against the hyperglycemic exacerbation of cardiac injury in the mouse model of reperfused myocardial infarction (MI).</p> <p><u>Methods:</u> Reperfused MI was performed in euglycemic (n=8) and hyperglycemic (n=7) C57Bl/6 wild-type (WT) mice, as well as in congenic euglycemic (n=11) and hyperglycemic (n=8) Jalpha18^{-/-} mice. MI consisted of 30 min coronary occlusions followed by 2 h reperfusion. Infarct size was determined by digital planimetry after TTC and Phthalo blue staining, and was reported as infarct size as percent area-at-risk (%A@R).</p> <p><u>Results:</u> Infarct size was reduced by 56% in euglycemic Jalpha18^{-/-} mice compared to euglycemic WT mice (18±3% vs. 41±5%, mean±SEM, p<0.05). Infarct size was also reduced in hyperglycemic Jalpha18^{-/-} mice compared to hyperglycemic WT mice, albeit to a much lesser extent (52±3% vs. 63±3%, p<0.05). Further, the areas at risk as percent of the left ventricular (LV) mass were similar for all groups (p=NS).</p> <p><u>Conclusions:</u> With regard to mechanism, these results clearly demonstrate that iNKT cells and innate immune responses contribute importantly to reperfusion injury. From a translational perspective, the results predict that interventions focused on suppressing the innate immune response during reperfusion will be significantly more effective in euglycemic patients than in those suffering from stress hyperglycemia.</p> | |
| 10 | <p>Gilbert Kinsey Programmed cell death 1 ligands promote resistance to renal ischemia reperfusion injury</p> <p>Ischemia reperfusion injury is a major contributor to acute kidney injury. The inflammatory response to ischemic injury, involving neutrophils and macrophages, compounds the renal cell death and loss of function. Recent studies have demonstrated that regulatory T cells (Tregs) suppress the immune response to kidney IRI and preserve renal function. Blockade of the co-inhibitory receptor programmed cell death 1 (PD-1) on the surface of Tregs negates their ability to protect from ischemic kidney injury. We hypothesized that one or both of the known PD-1 ligands must interact with PD-1 on Tregs and possibly other PD-1 expressing cells to mediate resistance to kidney IRI. To test this naïve C57Bl/6 mice were treated with a B7-H1 (PD-L1) blocking antibody, B7-DC (PD-L2) blocking antibody or an isotype control antibody 18 hr prior to mild bilateral renal ischemia. Kidneys were allowed to reperfuse for 18 hr then renal function and histology were assessed and accumulation of leukocytes was measured by flow cytometry. Compared to isotype control antibody treated mice after IRI (plasma creatinine (PCr) level: 0.5±0.2, n=3; sham PCr: 0.3±0.1, n=3) blockade of either PD-L1 (PCr: 1.1±0.4, n=3) or PD-L2 (PCr: 1.3±0.2, n=3) significantly enhanced renal functional impairment. Likewise, acute tubular necrosis assessed by H&E staining was markedly increased in the PD-1 ligand blocking antibody treated mice. Flow cytometric analysis of kidney infiltrating leukocytes revealed that blockade of either PD-1 ligand significantly enhanced accumulation of neutrophils (CD45+Live/Dead cell stain-negativeCD11b+GR-1high). These studies suggest that both PD-1 ligands participate in the natural defense against kidney IRI and that the PD-1 ligand interactions regulate innate immune responses to renal injury.</p> | Board |
| 11 | <p>Uta Erdbrugger Novel approach for characterizing circulating microparticles using imaging Flow Cytometry</p> <p>Microparticles (MPs) are submicron vesicles released from cell membranes in response to activation, cell injury or apoptosis. Circulating MPs in blood range in size from 100-1000nm and are believed to express proteins and phospholipids associated with their parent cells of origin and have become important biomarkers in many diseases. As such, not only has the quantification of these MPs become of</p> | Board |

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| | <p>interest, but also the characterization of their size and source has become equally important. The clinical importance of evaluating MPs has become increasingly recognized, although no standardized method exists for their measurement. Flow cytometry is the most commonly used technique, however because of the small size of MP and the limitations of current flow cytometry instrumentation in measuring biological particles in these size ranges accurate measurements are hampered by this methodology. We decided to investigate whether the use of flow cytometry combined with imaging, such as is possible with the Imagestream imaging flow cytometer, would be a more robust approach to characterizing circulating MPs.</p> <p>By combining flow cytometry with imaging we were able to demonstrate improved detection, phenotyping and absolute counting of MPs, while also providing morphological confirmation and the ability to distinguish true single events from cell debris or particle aggregation. Evaluating MPs below 200nm and sizing remain a challenge as some MPs remain below the detection threshold of the Imagestream imaging system and standardized biological calibrators remain to be developed.</p> | |
| 12 | <p>Quanjun (Trey) Cui Nano-Fullerol may prevent steroid-induced osteonecrosis by inhibiting adipogenic differentiation of bone marrow stem cells</p> <p><u>Introduction:</u> Use of high doses of corticosteroids is the most common cause of non-traumatic osteonecrosis of the femoral head (ONFH), a debilitating disease affecting young adults in their third decade of life. Successful treatment of ONFH is a big challenge to both scientists and clinicians due to difficulties in early diagnosis, its complex etiology and limited knowledge of its pathogenesis. Oxidative stress has attracted increasing attention in steroid-induced ONFH. Our previous study showed that dexamethasone (DEX) produces reactive oxygen species (ROS) that promote adipogenesis and inhibit osteogenesis in a mouse bone marrow stromal cell line, D1, and that the polyhydroxylated fullerene, fullerol, will antagonize the adipogenic activity of DEX on the cells from mouse bone marrow. This report aims to study the impact of fullerol on high dose DEX-induced adipogenesis in both rabbit and human bone marrow stem cells.</p> <p><u>Methods:</u> Fullerol was prepared in an aqueous solution and filtered through a 0.2 µm membrane before its use. The experiments with animals were conducted following IACUC approval. Rabbit bone marrow cells were flushed out of the cut ends of the femora of New Zealand white rabbits, and the stromal population was separated from hematopoietic elements by serial passaging of adherent cells. Cells were cultured in DMEM containing 15% FBS and maintained in an incubator at 37°C and 5% carbon dioxide. Human bone marrow cells were obtained commercially (Lonza). Cytotoxicity of fullerol and DEX was assessed by MTS assay. Sudan IV staining was used to characterize adipogenesis and gene expression was determined by real time RT-PCR.</p> <p><u>Results:</u> It was shown that treatment with either Dex (1 µM and 10 µM) or fullerol (0.1 µM and 1 µM) or their combination for 24 h had no toxic effect on primary rabbit bone marrow stromal cells. Fullerol could inhibit the expression of genes that encode markers of adipogenesis such as PPAR γ and AP2 in rabbit marrow cells and fullerol could prevent DEX-induced adipogenesis in primary stromal cell cultures from human bone marrow.</p> <p><u>Discussion:</u> Fullerenes have been characterized as “radical sponges”, and their antioxidative activity reported to be several hundred-fold higher than other antioxidants. This study showed that fullerol could inhibit adipogenesis induced by DEX in primary bone marrow stromal cells, suggesting that it may be considered for further investigation as a potential treatment to avert steroid-induced ONFH. Further in vivo study is necessary to provide evidence for this hypothesis.</p> | Board |
| 13 | <p>JoAnn V. Pinkerton Maintenance of the efficacy of desvenlafaxine in menopausal vasomotor symptoms: a 1-year randomized controlled trial</p> <p><u>Objective:</u> To assess 12-week efficacy of desvenlafaxine in a substudy of</p> | Board |

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| | <p>postmenopausal women who experienced at least 50 bothersome moderate to severe hot flushes per week at baseline enrolled in a year-long, double-blind, placebo-controlled safety trial.</p> <p><u>Methods:</u> Postmenopausal women were randomly assigned to receive placebo or desvenlafaxine 100 mg/d, titrated over the first week on-therapy. Primary outcomes were change from baseline in the number and severity of hot flushes at weeks 4 and 12. Secondary outcome was percent of women achieving minimal clinically important difference (MCID) in the number of hot flushes at week 12.</p> <p><u>Results:</u> The efficacy substudy population included 365 women (desvenlafaxine, n=184; placebo, n=181); 301 participants completed 12 weeks. Desvenlafaxine treatment significantly reduced both the average daily number of moderate to severe hot flushes and the daily hot flush severity score compared with placebo at weeks 4 and 12 (all P<0.001). At week 12, hot flush frequency for desvenlafaxine was reduced by 62% (-7.3 hot flushes per day) and severity by 25% for desvenlafaxine; placebo, 40% (-4.5 per day) and 12%, respectively. Median time to onset of efficacy (50% reduction in frequency) was 13 days for desvenlafaxine vs 48 days for placebo (P<0.001). The MCID, -5.35 moderate and severe hot flushes per day, was achieved by 68% of desvenlafaxine-treated women (placebo, 44%; P<0.001). A total of 22/200 (11.0%) desvenlafaxine-treated patients and 9/190 (4.7%) placebo-treated patients discontinued early due to adverse events; 7/200 (3.5%) and 24/190 (12.6%), respectively, discontinued due to lack of efficacy.</p> <p><u>Conclusions:</u> Women with bothersome moderate to severe hot flushes receiving desvenlafaxine achieved symptom reduction that was both statistically significant and clinically relevant based on an MCID analysis.</p> | |
| 14 | <p>Edward Perez-Reyes Development of drug-inducible gene therapies for the treatment of neurological disorders</p> <p>We have developed novel gene therapies that allow the expression of one or two genes of interest in a drug-inducible manner. These genes are packaged into adeno-associated viral (AAV) particles, which have proven safe for use in humans. Recently, the first AAV gene therapy was approved for use in Europe. We genetically engineered the AAV targeting vector to deliver a modified reverse tetracycline repressor transcription factor (rtTR) that turns on gene expression in the presence of very low concentrations of doxycycline (Dox). Doxycycline is approved for use in humans (as anyone who went to the clinic with a deer tick bite knows!). We have constructed a toolkit of short promoters to drive expression of the rtTR and validated their strength in neuroblastoma cells with a luciferase assay. We will show how we can titrate rtTR activity with the use of these promoters and how little expression there is in the absence of Dox. We will also present data on the use of different serotypes to infect the rodent brain, focusing on their ability to target the hippocampus and retrohippocampal formation. We will also present exciting preliminary data showing how expression of a potassium leak channel decreases seizures in a rodent model of temporal lobe epilepsy. These studies were performed in collaboration with Dr. Jaideep Kapur (Neurology). We would like to take this opportunity to invite other neuroscientists who are interested in gene therapy to discuss new targets and explore new collaborations. For basic science applications in rodents, we have also developed Cre- and dox-dependent AAV targeting vectors.</p> | Board |
| 15 | <p>Mark DeBoer Development of a sex- and ethnicity-specific childhood continuous metabolic syndrome risk score</p> <p><u>Background:</u> The metabolic syndrome (MetS) is a cluster of clinical indices that increase risk for Type 2 diabetes (T2DM) and cardiovascular disease (CVD). The diagnosis of MetS is based on cut-off points for these different components, including waist circumference (WC), triglycerides (TG), HDL cholesterol, blood pressure (BP), and fasting glucose. However, the best way to diagnose MetS in children remains unclear, and current attempts result in ethnic discrepancies.</p> | Board |

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| | <p>Methods: Using 1999-2008 data from the National Health and Nutrition Examination Survey (NHANES), we designed a childhood continuous MetS (CC-MetS) risk score that is sex- and ethnicity-specific. We did so by performing confirmatory factor analysis of a single MetS factor, allowing the individual components (WC, TG, HDL, BP, glucose) to vary by sex and ethnicity when these components were significantly different by sex/ethnic group in their contribution to the MetS factor. The ethnic divisions were non-Hispanic white (NHW), non-Hispanic black (NHB) and Hispanic (Hisp). This provided a MetS score that is unique to each sex/ethnic group in the weighting of each component to the final continuous score. We then used ROC curves to compare this CC-MetS score to traditional ATP III-based MetS score (ATP-MetS), corresponding to a z-score cut off of 0.75. Using this cut-off for each of the race/ethnicities we then compared the ability of this score vs. ATP-MetS to predict elevations in surrogate markers of T2DM and CVD risk: insulin, high sensitivity C-reactive protein (hsCRP), and uric acid.</p> <p>Results: We generated sex- and ethnicity-specific equations that differed in the contribution of HDL and TG to the final CC-MetS score, as determined by the factor analysis. This score was significantly more sensitive than ATP-MetS score at detecting >2 elevation among the surrogate markers: Males, ATP-MetS: NHW 56.3%, NHB 42.2%, Hisp 63.7%; CC-MetS: NHW 86.0%, NHB 75.6%, Hisp 75.6% (p<0.05). Females, ATP-MetS: NHW 25.4%, NHB 23.9%, Hisp 38.3%; CC-MetS 47.1%, NHB 64.7%, Hisp 81.2% (p<0.05).</p> <p>Discussion: These new equations for the CC-MetS score produce a clinically accessible and interpretable MetS score that is sex- and ethnicity-specific and that can be used to identify children at higher risk for developing adult diseases related to MetS, who could then be targeted for increased intervention. Additionally, they provide a powerful new outcome that can be utilized in childhood obesity and MetS research.</p> | |
| 16 | <p>Jennifer Charlton Urinary Biomarkers are Affected by Prematurity</p> <p>Background: Evidence suggests prematurity and low birth weight are associated with nephron deficits in the infant kidney, which increases the risk of developing hypertension and renal dysfunction in adulthood. Serum creatinine is a poor marker for renal injury and reserve. Thus, it is vital to discover other markers to monitor renal health and injury in a dynamically changing environment such as the developing infant kidney.</p> <p>Objective: Our goal was to determine the role of gestational age in the pattern of urinary protein excretion during postnatal maturation. Our aims were to: 1. Determine the normal changes in urinary protein excretion in term infants, 2. Identify if these proteins are altered in the premature infant, 3. Determine the effect of prematurity on the urinary proteome during renal maturation.</p> <p>Methods: Urine samples were collected at birth and at intervals coinciding with normal well child check ups over 12 months of age from healthy preterm (gestational age 33-35 weeks) and term infants (38-40 weeks). Urinary levels of IGFBP-1, IGFBP-2, IGFBP-6, MCP-1, Siglec-5 and CD14 were determined using a multiplex ELISA and normalized to sample's urine creatinine measurement.</p> <p>Results: The urinary concentration of IGFBP-1, IGFBP-2, IGFBP-6, MCP-1, Siglec-5 and CD14 was relatively stable over the first year of life in full term infants. The preterm infants had a significantly elevated amount of urinary IGFBP-1, IGFBP-6, Siglec-5 and CD14 (p-value<0.01) at birth. The levels declined in the preterm group over time and by two months there was no significant difference between the preterm and term infants. From two to 12 months of age there was no difference in the urinary concentrations of IGFBP-1, IGFBP-2, IGFBP-6, MCP-1, Siglec-5 and CD14 between the groups.</p> <p>Conclusion: Urinary concentrations of IGFBP-1, IGFBP-2, IGFBP-6, MCP-1, Siglec-5 and CD14 in healthy preterm infants are elevated at birth and remain elevated over two months compared to full term infants. This data has provided insight into normal developmental processes that may be altered when an infant is</p> | Board |

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| | born with a more severe degree of prematurity increasing the infant's risk for chronic kidney disease as an adult. Gestational age-dependent normal values are needed when considering biomarkers for childhood renal disease. | |
| 17 | <p>Jennifer Charlton Developmental Regulation of Retinol Binding Protein in the Kidney of Mice and Men <u>Background:</u> Vitamin A is critical in renal development and deficiency results in a reduction of nephron number. Retinol binding protein (RBP) stabilizes and transports the labile retinoid (vitamin A). RBP has been localized to the proximal tubule in the rat. Our group has demonstrated higher levels of urinary RBP in premature infants than term infants during late nephrogenesis that decrease with postnatal maturation. <u>Objective:</u> Determine the localization of RBP in the kidneys of mice and infants during late nephrogenesis and subsequent renal maturation. <u>Design/Methods:</u> Kidneys from C57B6 mice were harvested on day of birth (P0, n=3) and postnatal day 14 (P14, n=3). Kidney tissue was obtained postmortem from three premature infants (gestational ages 24, 30 and 37 weeks) and a 4 month old. None of the infants were known to have renal disease: causes of death were intraventricular hemorrhage, congenital heart disease and placental abruption. Kidney sections were stained with an anti-RBP antibody and examined by light microscopy. <u>Results:</u> In P0 mice, RBP first appeared below the nephrogenic zone in the cortical tubules in a punctate, vesicular pattern. By P14, RBP was no longer detectable in the tubules. In human infants at birth (24, 30 and 37 weeks gestation), the RBP pattern of staining was similar to the mouse kidney at P0 with a punctate, vesicular pattern in the cortical tubules, sparing the nephrogenic zone and medulla. By 4 months of age, RBP appeared in tubules throughout the cortex extending to the capsule. <u>Conclusions:</u> At birth, RBP appears in the maturing cortical tubules in both mouse and preterm infant, but not in the overlying nephrogenic zone. After completion of nephrogenesis, tubular RBP disappears in the mouse, but persists in the infant. It is significant to highlight that premature infants have high levels of RBP detectable not only in their urine, but is also within the proximal tubule as early as 24 weeks, representing the infant's ability to recirculate RBP at a very young gestational age."</p> | Board |
| 18 | <p>Bradford C Bennett Enhancing AFO Efficacy through Continuous, Non-Evasive Gait Assessment Individuals with mobility disabilities as a result of cerebral palsy (CP) are often prescribed ankle foot orthoses (AFOs) to aid in their walking and prevent muscle contractures. More than 50% of the estimated 764,000 people with another 9500 children diagnosed each year. in the United States who have one or more symptoms of CP are prescribed orthoses, with significantly larger numbers worldwide. Despite this widespread use of AFOs, current methods for evaluating - and ultimately enhancing - their efficacy in this population are limited. Most studies of gait changes with AFO use are based on single visit data collections in the gait lab, which only reveal short-term improvements in gait mechanics and do not address the AFOs' larger goals of increasing activity and participation in school and society and preventing muscle contractures and bony deformities. Accessing such data would provide insight into the efficacy of current AFOs and guidance for future AFO development, but longer-term, more continuous data collections in the wearers' natural environments are necessary. The proposed project seeks to address these limitations of solely relying on in-clinic data collections by addressing the fundamental scientific and technical challenges to the non-invasive and continuous collection and analysis of gait and activity data in any location over an extended period of time. Accelerometers, gyroscopes, microcontrollers, non-volatile memory, batteries, and supporting circuitry will be molded into AFOs, sensing, pre-processing, and storing movement data that is later downloaded and post-processed to determine both the amount and type of activity</p> | Board |

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| | <p>(e.g. walking vs. running vs. crawling) and various spatial-temporal gait parameters (e.g. stride length, ankle angle, etc.).</p> <p>This objective, long-term, patient-specific assessment of AFO efficacy will transform the way doctors and gait specialists prescribe and monitor AFO use and will inform the development of future AFO technologies. For the first time clinicians will be able to follow the real world progress of the effect of AFO use. The sensing system is completely non-invasive as it will reside in the AFOs themselves, and the effect on day-to-day performance of different AFOs can be studied. Limitations that affect behavior (e.g. stair climbing) can be documented, and ankle position will be recorded as a function of time so that it can be determined if desired positions are held long enough to prevent contractures and deformities. If AFO use results in decreased walking performance or limits other activities, the clinician can modify the AFO, prescribe a different type of AFO (e.g. hinged vs. solid), or can suggest that the AFOs only be worn part of the time or not at all.</p> <p>This work - which brings together an orthopedics and gait biomechanics specialist, a body sensor networks expert, and an orthopedic surgeon - will make several scientific and technical advancements in the fields of motion analysis and assistive technologies for CP. First, this work advances the area of long-term, non-invasive movement data collection and analysis. Increasingly, clinicians are using evidence-based interventions and are interested in quantitative measures in daily life, outside of the clinic or laboratory. This work goes beyond the mere measurement of general activity or number of steps (as is provided by existing off-the-shelf technologies) in that it will provide activity classification and spatial-temporal gait parameters. Second, the resulting knowledge of how an individual child is moving in the world with his/her AFOs will provide feedback as to the appropriateness of the devices, enabling changes to the AFOs to be made as necessary. Finally, the results of this analysis will provide insights into opportunities for future AFO development.</p> <p>The impact of this work spans improved basic understanding of activity to improved quality of life for individuals with walking disabilities. While this work focuses on aiding those with CP, the basic science of this work can be applied to AFOs for individuals with different disabilities as well as the ability to non-invasively and continuously measure the movement of other body segments/joints. In addition, this work will develop technology that will provide information that will be needed in the future when active devices come into practice. Finally, with improved batteries and electronics it will become feasible to build sensors into every AFO so that gait/activities could be monitored intermittently to assess performance changes over time without a lab visit.</p> | |
| 19 | <p>Arthur Weltman Acute isoenergetic moderate- and high-intensity exercise improves insulin action in pre-diabetic adults</p> <p>PURPOSE: We examined the effects of acute isoenergetic moderate (MIE) and high intensity (HIE) exercise on insulin action in seventeen sedentary pre-diabetic adults (8 males/9 females; age=49yrs; BMI=32.4 kg/m²; fasting glucose=106 mg/dl; 2-hour glucose= 173 mg/dl; A1c= 5.7%).</p> <p>METHODS: Subjects completed 3 conditions with order randomized: MIE (50% VO₂peak), HIE (82% VO₂peak), and seated rest (Control). Exercise energy expenditure was equated to 200-kCal. One-hour post-exercise (or control), subjects received a 3-hr, 75-gram oral glucose tolerance test (OGTT). Plasma glucose and insulin concentrations were measured before and at frequent intervals after glucose ingestion. The oral minimal model, which incorporates the plasma glucose and insulin response observed during the OGTT and the glucose dose were used to derive insulin sensitivity (SI).</p> <p>RESULTS: Compared to control, insulin sensitivity was increased by 22% (p = 0.04) and 30% (p = 0.002) after MIE and HIE, respectively. There were no differences in SI between the exercise conditions (p=0.36). The improvement in insulin action corresponded to reductions in the incremental area under the curve</p> | Board |

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| | <p>(AUC) for glucose previously reported by our group [compared to control 3-hr glucose AUC decreased by 13.9% (p=0.03) and 21.4% (p<0.001) after MIE and HIE, respectively].</p> <p>CONCLUSION: These results demonstrate that changes in SI occur early in the recovery period after a single bout of exercise (at least 1-hour after the cessation of exercise) and that when calorically equated, both moderate and high intensity exercise are effective for improving SI in pre-diabetic adults.</p> | |
| 20 | <p>Dongfeng Pan A Novel Tumor-targeting Small Molecule PET/Fluorescence Dual Imaging Probe <u>Objective:</u> To synthesize and develop a novel tumor-targeting small molecule PET/fluorescence dual imaging probe <u>Methods:</u> Tumor-specific heptamine-cyanine dye was conjugated with DOTA and radiolabeled with Cu-64 for dual-modality imaging. Detailed spectroscopic properties of the probe PC 1001 were obtained. <i>In vitro</i> cellular uptake studies were performed in tumor (MCF-7) and non-tumor (MCF-10A) cells to establish tumor-specific selectivity. Inhibition studies for tumor-specific uptake were performed to offer plausible mechanism of action. <i>In vivo</i> fluorescence and PET imaging of breast tumor xenograft in mice at various time points were carried out and analyzed. Blood clearance (half-life in blood), biodistribution, tumor-specific uptake and plasma binding were demonstrated in quantitative manner. <i>Ex vivo</i> histology (H/E staining) and confocal fluorescence imaging were examined at microscopic level. <u>Results:</u> The conjugation of DOTA-Cu moiety to heptamethine cyanine dye remained similar fluorescence properties $\epsilon=82,880 \text{ cm}^{-1}\text{M}^{-1}$, $E_x/E_m=750/820 \text{ nm}$ as that of the original dye indicating no significant effect on optical properties upon PET probe attachment. Time-dependent cellular accumulation suggested significantly higher probe uptake (>2-fold) in MCF-7 tumor cells than in control MCF-10A epithelial cells. Inhibition studies revealed the possible mechanism to be organic anion transport polypeptide (OATP) mediated uptake. Dual-modality PET/fluorescence imaging by the probe demonstrated desirable accumulation in tumor sites. SUV analysis of tumor versus muscle (control) suggested a factor of 5.8 ± 0.2 fold increase in uptake over 48 h post probe injection. Blood clearance half-life of the probe was observed to be $257\pm 13 \text{ min}$. Microscopic fluorescence imaging of <i>ex vivo</i> harvested tissue indicated that the probe was mainly associated with viable tumor but not with necrotic tissue. <u>Conclusion:</u> A highly effective dual-modality (PET/fluorescence) imaging probe is obtained, and its feasibility for tumor-specific imaging is demonstrated. The results indicate that the probe is well-suited to advance into pre-clinical evaluation.</p> | Board |
| 21 | <p>Dongfeng Pan cFLFLF-PEG-HYNIC-99mTc, a novel nuclear probe for Imaging Acute Osteomyelitis: non-invasive imaging of inflammation/infection <u>Objective:</u> Development of molecular imaging probes for detection/diagnosis of inflammation/infection via FPR receptors. <u>Methods:</u> FPR receptor specific peptide antagonist cinnamoyl-phenylalanine-D-leucine- phenylalanine-D-leucine-phenylalanine [cF(D)LF(D)LF] derivative is synthesized and decorated with variety of molecular imaging tools; e.g. optical (Cy-7) and radionuclear (^{64}Cu, $^{99\text{m}}\text{Tc}$) by linking with polar pegylated linker for optimizing pharmacological properties. The cFLFLF based molecular imaging probes were tested in various animal models of infections and acute inflammation injury: for example Lung pneumonia infection, osteomyelitis infection, ear irritation/pain, lung and heart ischemic reperfusion, and inflamed diabetic pancreas. <u>Results:</u> The results from the studies in variety of animal infection/inflammation models indicated that cFLFLF is indeed very promising molecular agent which targets FPR receptors on activated leukocytes. The modification of structure results in varying pharmacological properties to deliver the probe by various modes of administration.</p> | Board |

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| | <p>Conclusion: An effective molecular imaging agent is developed for detection/diagnosis of acute inflammation and infection wherein leukocytes as an innate immune response is triggered.</p> | |
| 22 | <p>Gary K. Owens Identification of a Stable Epigenetic Marker of Cell Lineage Identified using a Novel Method for Detecting Histone Modifications of Specific Gene Loci in Single Cells in Histological Sections Chromatin immunoprecipitation (ChIP) assays have contributed greatly to our understanding of the role of histone modifications in regulation of gene expression. However, a major limitation is that they do not permit analysis of histone modifications at a given gene locus within individual cells thus confounding interpretation of analyses of heterogeneous cell populations, and precluding direct assessment of the role of histone modifications within individual cells within complex multicellular tissues. Herein we present a new method which permits visualization of histone modifications of a single genomic locus with single-cell resolution in formaldehyde-fixed paraffin-embedded tissue sections based on combined use of In Situ Hybridization and Proximity Ligation Assay (PLA) for detection of a biotinylated probe hybridizing the gene locus and the histone modification of interest. This method was used to test the hypothesis that H3K4dime of the MYH11 gene locus is a specific signature for smooth muscle cells (SMCs) and persists even when these cells undergo de-differentiation. We show the feasibility and reliability of ISH/PLA as a new method for studying histone modifications and provide compelling evidence that H3K4dime of the MYH11 locus is restricted to the SMC lineage in vivo. This new methodology has promise for broad applications in the study of epigenetic control mechanisms in complex multicellular tissues in development and disease.</p> | Board |
| 23 | <p>Sara F. Sutherland Variation in symptoms, oxygen saturation and resting heart rate in trekkers subjected to rapid ascent and descent without prior acclimatization <u>Study objectives:</u> Travelers enjoying mountain sports such as trekking typically arrive at altitude with minimal acclimatization. We conducted this study to quantify the correlation between rapid ascent, symptoms (SYM), BP, oxygen saturation (O2SAT) and heart rate (HR). <u>Methods:</u> This prospective observational study was conducted during an organized trek in Nepal where participants starting at an elevation of 4590 feet on day 1, hiked to an elevation of 17,257 feet on day 7 before returning to 4590 feet on day 13. Because the trek returned on the same path, measurements were made at the same altitude in either direction to assess acclimatization. Participants were healthy volunteers who had been medically cleared for the trek prior to departure. Participants completed the Lake Louise Score (LLS) for the diagnosis of Acute Mountain Sickness (AMS), and had O2SAT, HR and BP recorded at the highest and lowest elevations for the day. Statistical analysis was performed using Pearson's correlation coefficient and the Mann-Whitney U test. <u>Results:</u> A total of 13 participants completed the study. The mean O2SAT at 4590 feet was 96% compared with 76% at 17257 feet. Mean O2SAT at 11300 (on days 3 and 10) was higher (93% vs. 89%) and HR lower (73 vs. 94) on the return trek (p<0.01). Correlation between O2SAT and HR was high (r=-0.82). Correlation between altitude and O2SAT was weak (r=0.25) and between altitude and heart rate was moderate (r=0.57). AMS was most prominent during the early part of the trek, with a mean O2SAT of 84% in those with AMS. Early desaturation was predictive of AMS several days before symptom onset. <u>Conclusion:</u> Significant desaturation is observed in healthy trekkers hiking to 17257 feet. HR and O2SAT are highly correlated, and acclimatization was evident in 7 days. Although a very small group experienced symptoms of mild mountain illness, these same trekkers had higher HR and lower pulse O2SAT compared with the main group at lower altitudes. Participants in high altitude recreational activities can monitor their heart rate as an indirect measure of acclimatization."</p> | Board |

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| 24 | <p>Janet V. Cross Macrophage Migration Inhibitory Factor promotes tumor growth and metastasis by inducing Myeloid Derived Suppressor Cells in the tumor microenvironment</p> <p>The inflammatory cytokine, Macrophage Migration Inhibitory Factor (MIF) is a critical mediator of numerous inflammatory disease processes. In addition, MIF is overexpressed in many cancers and the degree of expression correlates with tumor aggressiveness. We identified MIF as a target for direct inhibition by a cancer preventive agent prevalent in broccoli. Based on this observation and the correlation between MIF expression and poor prognosis in human patients, we set out to determine how MIF might contribute to tumor growth and progression. We hypothesized that, as an inflammatory cytokine, MIF would regulate the interaction between the tumor and the host immune response, rather than impacting an intrinsic property of the tumor cells. To test this, we used the syngeneic 4T1 model of breast carcinoma. This model recapitulates many aspects of human breast tumor progression, including spontaneous metastasis from the mammary fat pad to similar target organs. We found that MIF expression in the tumor cells increased tumor growth and metastasis in an orthotopic tumor model. Importantly, the MIF dependent growth differences are only manifested in vivo, as the MIF depleted cell line was not compromised in growth or colony formation in vitro, suggesting that MIF may contribute to the interaction between the tumor and the host immune response. This was confirmed by demonstrating that MIF depleted and MIF containing tumors exhibited similar growth and metastasis properties in immunodeficient animals. Evaluation of the immune cell infiltrates in the MIF containing and MIF deficient tumors revealed that the abundance of a highly immune suppressive subpopulation of myeloid derived suppressor cells (MDSCs) within the tumor is dependent on MIF expression. In vitro, tumor conditioned media from MIF expressing cells promoted the differentiation of myeloid cells into the same population of MDSCs. The MIF inhibitor that we characterized inhibited the abundance of monocytic MDSCs in the tumor in vivo and blocked the MIF dependent differentiation in vitro. Finally, we demonstrated that depletion of MDSCs abolishes the impact of MIF on tumor growth, suggesting that these cells are critical for MIF to mediate its effects. We are currently exploring the mechanisms by which MIF controls the abundance of monocytic MDSCs in the tumor microenvironment and how this relates to promotion of tumor metastasis. Our work establishes MIF as a potentially valuable therapeutic target in tumor metastasis and supports a potential alternative mechanism for cancer prevention by MIF inhibitors through targeting the inflammatory tumor microenvironment.</p> | Board |
| 25 | <p>Nathan Charlton The Epidemiology of Caving Injuries in the United States</p> <p><u>Objective.</u> Caving is a demanding sport practiced throughout the world. Currently, there is no collective data analyzing injury mechanism or type in these austere environments. This study is a retrospective analysis of caving incidents documented by the National Speleological Society (NSS) - American Caving Accidents (ACA) annual publication.</p> <p><u>Methods.</u> This study retrospectively analyzes 877 incident reports collected between 1980 and 2008 by NSS-ACA. For each victim, the month, year, location, age, gender, incident type, injury zone of the body, injury type, the result of the incident, and time intervals for rescue were extracted.</p> <p><u>Results.</u> A total of 1356 victims were identified, 83% of victims were male, 17% female. Average age: 26 years for males and 27 years for females (range 2-69 years). The greatest number of events occurred in summer months, peaking in July. The most common incident leading to traumatic injury was a Caver Fall (74%), also contributing to 30% of caver fatalities. Lower extremities were most commonly injured (29%), followed by the upper extremities and head (21% and 15%, respectively). Fractures comprised 41% of injuries, followed by lacerations</p> | Ednam |

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| | <p>(13%), bruise/hematoma/abrasions (12%), and sprains/strains (7%). <u>Conclusion.</u> The majority of injuries were not life threatening, however, over 28 years there were 81 documented fatalities. Similar to other studies of wilderness injuries, fractures, soft tissue injuries and lacerations were prominent in this study. In general, the overall precipitating event leading to injuries is falling, leading to orthopedic trauma. To better prepare cave rescue teams we have attempted to describe the characteristics of caving injuries in the United States.</p> | |
| 26 | <p>Nathan Charlton U.S. Caving Fatalities from 1980 – 2008 <u>Background.</u> Caving is a demanding sport practiced throughout the world. Currently, there is no collective data analyzing mechanism of fatalities in these austere environments. This study is a retrospective analysis of caving fatalities documented by the National Speleological Society (NSS) - American Caving Accidents (ACA) annual publication. <u>Methods.</u> This study retrospectively analyzes 877 incident reports collected between 1980 and 2008 by NSS-ACA. For each victim, the month, year, location, age, gender, incident type, injury zone of the body, type of injury, result of the incident, and time intervals for rescue were extracted. <u>Results.</u> 81 fatalities were identified, 84% of victims were male, 16% female. Average age: 29 years for males, 27 years for females (range 10 - 59). The average incidence was 3 deaths/year (range 0-9). There were no significant trends seen in incidents per month or incidents per year throughout the course of the study. The most common mechanisms leading to death were Caver Fall and Drowning (30% each). Cardiac disease was the most common medical illness, accounting for 11% of deaths. Of traumatic injuries, diffuse/generalized trauma and head injury accounted for the largest percentage of fatalities at 37% and 33%, respectively. Inexperience clearly contributed in 26% of fatalities. 85% of all fatalities occurred prior to rescuer arrival, only 2% survived until after rescue. <u>Conclusion.</u> There were 81 documented fatalities over this study period. Similar to other studies of mortality in the wilderness, falling, drowning and other traumatic injuries were the most common causes of death. Cardiac disease resulted in the greatest number of medically related deaths. Many fatalities appeared to be from caver inexperience. As the majority of deaths occurred prior to rescuer arrival, it appears that cavers themselves are the key to reducing fatalities. They must be well prepared and well trained to minimize risk and promote safety."</p> | Ednam |
| 27 | <p>Susanna R. Keller Distinctive roles of Rab GAPs AS160 and Tbc1d1 in skeletal muscle and adipocyte glucose uptake and whole body glucose homeostasis Insulin increases glucose uptake in skeletal muscle and adipocytes and thus facilitates the disposal of ~90% of glucose after a meal. The increased glucose uptake is achieved through the translocation of the glucose transporter GLUT4 from an intracellular compartment to the cell surface. Recent studies have implicated two Rab GTPase activating proteins (Rab GAPs), AS160 and Tbc1d1, in regulating glucose uptake and GLUT4 subcellular distribution. To determine the roles of the Rab GAPs in GLUT4 subcellular distribution, glucose uptake, and whole body glucose homeostasis, we obtained AS160 and Tbc1d1 knockout (KO) mice. Our results with isolated adipocytes and skeletal muscles suggest that the two Rab GAPs play distinct roles; in AS160 KO glucose uptake is impaired in adipocytes and soleus, but not in extensor digitorum longus (EDL), while in Tbc1d1 KO glucose uptake is impaired in EDL, but not in adipocytes and soleus. Simultaneously, GLUT4 is downregulated in adipocytes and soleus of AS160 KO and in EDL of Tbc1d1 KO mice and GLUT4 cell surface expression is regulated similarly in AS160 KO soleus and Tbc1d1 KO EDL. Subcellular fractionations show impaired GLUT4 subcellular distribution in both AS160 and Tbc1d1 KO in gastrocnemius/quadriceps, suggesting roles for both in large skeletal muscles. Insulin and glucose tolerance are impaired in AS160 KO mice and normal in Tbc1d1 KO mice. These data suggest differential roles for AS160 and Tbc1d1 in</p> | Ednam |

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| | the regulation of glucose uptake in different skeletal muscles and adipocytes and in the control of whole body glucose homeostasis. | |
| 28 | <p>Alexander L Klibanov Targeted microbubbles - ultrasound contrast agents for molecular imaging and drug delivery</p> <p>Ultrasound is a unique imaging modality that combines real-time monitoring with portable inexpensive equipment as well as the ability to guide biopsies and therapeutic interventions. Ultrasound can also provide field focusing in the areas of disease, to achieve ablation. Use of ultrasound contrast materials, such as microbubbles, provides additional functionality, including targeted (molecular) imaging, triggered drug and gene delivery.</p> <p>Microbubble agents are biocompatible micrometer-size intravascular contrast materials. They are prepared by self-assembly from perfluorocarbon gas and stabilized by a phospholipid monolayer shell with a PEG brush coating. On the distal tips of the brush polymer we attach targeting ligands, such as antibodies, peptides, peptide mimetics, and carbohydrates. These ligands provide microbubble adhesion and retention at the surface of activated vascular endothelium in the areas of disease, such as ischemia-reperfusion injury, active thrombi, inflammation or angiogenesis (i.e., tumor vasculature). Circulating microbubble contrast rapidly clears from the bloodstream, therefore, targeted imaging can be performed within minutes. Detection sensitivity of circulating, as well as targeted, ultrasound contrast material is excellent - individual microbubbles, with sub-picogram mass can be detected, with sub-mm spatial resolution, in real time.</p> <p>Microbubble-based drug and gene delivery is based on the compressibility of gas core and its mechanical response to the ultrasound pressure field. Microbubbles are destroyed by focused high pressure ultrasound, resulting in therapeutic bioeffects. Targeted transfection can be achieved in the area of ultrasound focus. Microbubble-liposome complexes can release entrapped drug during ultrasound treatment.</p> <p>Overall, medical application of microbubble technology can bring novel diagnostic and therapeutic approaches combined with ease of use and low cost.</p> | Ednam |
| 29 | <p>Chien Li Regulation of insulin secretion by vesicular nucleotide transporter mediated ATP signaling</p> <p>Type 2 diabetes (T2D) is a multifactorial disorder characterized by dysregulated insulin secretion and insulin resistance in peripheral tissues. T2D may be caused by a number of lifestyle factors, yet obesity is the primary risk factor in individuals with a genetic predisposition. Consuming a high fat diet leads to excessive energy intake and consequent obesity. Currently the mechanisms underlying β cells dysfunction associated with excessive nutrient intake and obesity remain elusive. We have determined elevated levels of vesicular nucleotide transporter (VNUT) in MIN6 cells, a mouse β cell line, treated with high fat media as well as in pancreatic islets isolated from mice fed with a high fat diet. VNUT is a recently identified vesicular transporter in adrenal chromaffin cells and is responsible for transporting ATP into secretory vesicles for storage and release. It has been shown that ATP is present in insulin secretory vesicles and ATP can regulate insulin release via purinergic signaling, yet the mechanism of ATP accumulation into insulin vesicles remains unknown. To probe the functional role of elevated VNUT expression in pancreatic β cells, we generated a VNUT overexpressing lentivirus. Overexpressing VNUT in β cells resulted in enhanced ATP release, as measured by a luciferase-based assay. Furthermore, overexpression of VNUT in isolated mouse islets resulted in significantly elevated basal insulin levels with reduced sensitivity to glucose stimulation in insulin secretion. Moreover, pretreating islets with suramin, a purinergic receptor antagonist, completely reversed enhanced basal insulin secretion induced by VNUT overexpression. On the other hand, knocking down (KD) VNUT expression with a VNUT-specific short hairpin RNA (shRNA) lentivirus suppressed ATP release from β cells. Intriguingly, we saw</p> | Ednam |

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| | <p>suppression of both basal and glucose-induced insulin secretion in VNUT shRNA lentivirus infected islets compared to that of control islets. Moreover, treating VNUT KD islets with ATP significantly increased insulin secretion. This suggests that the reduced insulin secretion observed in VNUT KD islets is due, at least in part, to reduced extracellular ATP signaling. In summary, our study reveals that VNUT is expressed on insulin secretory vesicles in pancreatic β cells and plays an important and novel role in ATP release which consequently modulates insulin secretion through purinergic signaling.</p> | |
| 30 | <p>Roberto Fernandez Cortical Responses to Visual Motion Reveal Distinct Effects of Aging and Alzheimer's Disease</p> <p>Optic flow (OF) is the radial pattern of visual motion that guides self-movement and supports navigation. Our previous work has demonstrated that impaired OF processing is associated with navigation impairments in Aging and Alzheimer's disease (AD). We have now used OF event related potentials (ERPs) to identify distinct cortical processing deficits in older adults and patients with early AD. Young (YNC) and older normal controls (ONC), and patients in the early stages of AD (EAD) observed sequences of OF stimuli during the recording of cortical responses. Each trial consisted of 9-15 randomly selected OF stimuli of either centered or laterally displaced focus of expansion (FOE) to simulate different heading directions. Upward or downward vertical motion stimuli prompted a rapid push-button response at the end of each trial. This helped focus the subject's attention on motion stimuli and allowed us to simultaneously record behavioral and ERP responses.</p> <p>We tested five forward self-movement heading simulations. When stimuli were preceded by random dots, YNC and ONC subjects showed robust N200 responses to all OF stimuli, regardless of the simulated heading. Subsequent stimuli evoked successively smaller responses, especially in EADs. The first responses showed remarkable differences across subject groups: All older subjects (ONC and EAD) showed significantly longer N200 response latencies compared to YNC. In contrast, EAD subjects had significantly smaller N200 amplitudes compared to those of YNCs or ONCs.</p> <p>In the vertical motion discrimination task, EADs were significantly less accurate at ~71% correct. The YNCs were significantly faster, with response times ~600 ms, with the ONCs at ~715 ms, and the EADs at ~860 ms. Task evoked ERPs had had the additional N2b and P300 waves following the N200. The N200 response was of equal latency in all subject groups, but of smaller amplitude in EAD. In EADs, the N2b was distinct from the small N200 waveform, more prolonged than N2bs in YNCs and ONCs, and followed by a smaller P300.</p> <p>To assess the behavioral relevance of the three vertical motion ERP components of ONCs and EADs, we used a stepwise multiple linear regression of vertical motion response times and percent detections. In ONCs and EADs, vertical motion response times relied only on N2b amplitudes ($F_{1,26} = 7.26$, $p = .012$, $\beta_{std} = .47$). In contrast, vertical motion percent detections relied only on N200 amplitudes ($F_{1,26} = 14.43$, $p = .001$, $\beta_{std} = .60$). This suggests that the effect of aging on response times is mainly related to attentional factors, whereas the effect of AD on motion detection is mostly related to sensory responsiveness.</p> <p>Our results suggest that responses evoked by OF stimuli can distinguish the effects of aging and AD on visual cortical motion processing. Aging results in delayed signal processing, while AD is associated with decreased cortical-sensory responsiveness.</p> | Ednam |
| 31 | <p>Stuart S. Berr PET imaging of tumor associated macrophages using mannose coated 64Cu liposomes</p> <p>Macrophages within the tumor microenvironment (TAMs) have been shown to play a major role in the growth and spread of many types of cancer. Cancer cells produce cytokines that cause macrophages to express scavenger receptors (e.g.</p> | Ednam |

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| | <p>the mannose receptor) and factors that facilitate tissue and blood vessel growth, suppress T cell mediated anti-tumor activity, and express enzymes that can break down the extracellular matrix, thereby promoting metastasis. We have designed a mannosylated liposome (MANLIPs) and show that it accumulates in TAMs in a mouse model of pulmonary adenocarcinoma. These liposomes are loaded with ⁶⁴Cu to allow tracking by PET imaging, and contain a fluorescent dye in the lipid bilayer permitting subsequent fluorescence microscopy. We injected these liposomes into a mouse model of lung cancer. In vivo PET images were acquired 6 h after injection followed by the imaging of select excised organs. MAN-LIPs accumulated in TAMs and exhibited little accumulation in remote lung areas. MAN-LIPs are a promising new vehicle for the delivery of imaging agents to lung TAMs. In addition to imaging, MAN-LIPs hold the potential for delivery of therapeutic agents to the tumor microenvironment.</p> | |
| 32 | <p>Laura Jansen Patterns of PI3K/AKT/mTOR Pathway Activation Differentiate Genetically Distinct Forms of Hemimegalencephaly <u>Rationale:</u> Hemimegalencephaly (HMEG) is a highly epileptogenic developmental brain malformation associated with enlargement of an entire cerebral hemisphere. Pathologically, cytomegalic and dysmorphic neurons, astrogliosis, dyslamination, and polymicrogyria are seen. Previous studies have suggested abnormalities in the phosphatidylinositol-3-kinase (PI3K)/AKT/mTOR pathway in HMEG. In the present study we performed detailed immunohistochemical and genetic analyses of human HMEG tissue to further delineate involvement of this pathway. <u>Methods:</u> Five children with HMEG were evaluated by standard protocols and underwent resective surgery for intractable epilepsy. Double-label fluorescence immunohistochemistry studies were performed using formalin-fixed, paraffin-embedded sections (4 μm) of resected cortex. Antibodies directed against the phosphorylated forms of AKT and ribosomal protein S6 were analyzed in conjunction with neuronal (MAP2) and glial (GFAP) cellular markers. DNA was isolated from specimens frozen at the time of surgery and subjected to sequence analysis using methods sensitive for detection of genetic mosaicism. <u>Results:</u> All specimens demonstrated increased phospho-S6 immunofluorescence in a subset of neurons, which ranged from less than 10% to nearly 100% of the total neuronal population. Varying degrees of phospho-S6 immunofluorescence were also identified in glial cells in all specimens. However, neuronal labeling with antibodies against phosphorylated proteins upstream of S6 in the PI3K/AKT/mTOR pathway was present in some patients but not others, suggesting the presence of abnormal activity at different levels of the pathway. Indeed, activating mosaic mutations in two different pathway components, the catalytic subunit of PI3K and of AKT3, were identified in patients with different immunohistochemical patterns. <u>Conclusions:</u> Our studies indicate that HMEG is a heterogeneous condition that may be caused by mosaic activating mutations of different members of the PI3K/AKT/mTOR pathway. Different genetic forms of this malformation may also be identified by patterns of immunohistochemical labeling. These findings suggest that therapies targeting abnormal activity at different levels of the PI3K/AKT/mTOR pathway could be beneficial for children with intractable epilepsy due to HMEG.</p> | Ednam |
| 33 | <p>Adam Goldfarb Iron Restriction Via PKC Signaling Critically Contributes to Erythroid PU.1 Dysregulation in Anemia of Chronic Inflammation In addressing factors that suppress erythropoiesis in anemia of chronic inflammation (ACI), we previously showed that iron restriction sensitizes cultured human erythroblasts to the inhibitory effects of inflammatory cytokines including interferon γ (IFNγ). This sensitizing effect was reversed by addition of isocitrate to cultures, and in a rat arthritis ACI model intraperitoneal injections of isocitrate completely and durably reversed anemia through in vivo stimulation of erythropoiesis. New studies using cultures of human hematopoietic progenitor cells (huHPC) have explored the signaling mechanisms by which iron and isocitrate</p> | Ednam |

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| | <p>modulate erythroid responsiveness to IFNγ. No impact of iron restriction or isocitrate treatment could be seen on IFNγ activation of STAT1 phosphorylation on tyrosine 701 or on serine 727. Similarly, iron restriction and isocitrate had no effects on IFNγ-mediated upregulation of STAT1 protein, STAT2 protein, IRF8 protein, or IRF9 mRNA levels. These findings suggest that iron and isocitrate do not affect the classical JAK1-STAT1-IRF1 or the alternative GATE-IRF9 pathways. We then examined expression of the transcription factor PU.1, a master regulator whose levels dictate myeloid versus erythroid cell fate in hematopoietic progenitors. Libregts et al., recently demonstrated that IFNγ upregulated PU.1 erythroblasts via IRF1. Our results showed that iron restriction potently augmented IFNγ induction of PU.1, by 2-3-fold, and also induced PU.1 on its own to a lesser degree. Importantly, isocitrate abrogated the upregulation of PU.1 caused by iron restriction. Furthermore, qRT-PCR on sorted erythroblasts from rat marrows showed increased PU.1 expression in animals with ACI and normalization of erythroid PU.1 expression in association with isocitrate treatment. Pop et al., have recently shown that downregulation of PU.1 early in erythropoiesis constitutes a key step in lineage commitment. Therefore we examined the kinetics of PU.1 expression in the huHPC model system. As expected, huHPC downregulated PU.1 during the initial 2-4 days of standard erythroid culture. Similar downregulation occurred in the presence of IFNγ, under iron replete conditions. However, with the combination of IFNγ and iron restriction, PU.1 levels remained high the entire culture period and showed minimal downregulation. Several experimental approaches addressed the erythroid developmental stages affected by iron restriction and IFNγ. Flow cytometry with intracellular staining showed that iron and isocitrate influenced IFNγ induction of PU.1 at an early CD34+ CD36+ stage. These findings were corroborated by immunoblot analysis of sorted progenitors showing iron restriction and isocitrate to affect PU.1 levels within CD36+ GPA- erythroid progenitors; the later CD36+ GPA+ progenitors showed extinction of PU.1 expression regardless of culture conditions. Finally, using purified CD36+ cells as a starting population, iron restriction and IFNγ again cooperated in induction of PU.1, with isocitrate reversing this effect. Prior studies from our lab have shown that erythroid iron restriction results in hyperactivation of PKCα/β. In addition PKCα/β is known to directly phosphorylate and activate PU.1. We therefore sought to determine whether PKC contributes to cooperative upregulation of PU.1 in erythroid progenitors subjected to iron restriction and IFNγ. Supporting this notion, the pan-PKC inhibitor BIM abrogated the effects of iron restriction plus IFNγ on PU.1 upregulation. Importantly, the dosage of BIM employed had no effect on viability or differentiation. Our findings thus define a pathway in which iron restriction and IFNγ act in a cooperative manner on early erythroid progenitors to increase PU.1 expression and interfere with its normal downregulation. Iron restriction and isocitrate exert their influences, at least in part, through alteration of PKC activation. We propose a model of ACI in which iron restriction and inflammatory signaling are both required to attain a critical threshold of erythroid PU.1, which may then interfere with early stages of lineage commitment. Through its reversal of PKC activation by iron restriction, isocitrate may act to keep PU.1 levels below this critical threshold.</p> | |
| 34 | <p>Lisa Pastore Longitudinal Interviews of Couples Diagnosed with Diminished Ovarian Reserve Undergoing Fragile X Premutation Testing <u>Background:</u> 10% of infertile women are diagnosed with diminished ovarian reserve (DOR), which greatly reduces the likelihood of pregnancy using her own ovum. Genetic testing may provide a reason for her early ovarian aging and/or have reproductive implications if she uses her own eggs. <u>Methods:</u> In this qualitative study, 7 DOR females and their husbands were interviewed individually regarding the experience of having genetic testing in the context of their reproductive decision-making. Three interviews were conducted (before/after learning the test results). <u>Results:</u> For women, their pregnancy-seeking journey was long and exhausting.</p> | Ednam |

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| | <p>Women understood the reproductive implications of being an FMR1 carrier, and hoped for a negative result. Being offered a genetic test caused women to pause and re-think their future reproductive plans. Husbands viewed the infertility journey as filled with unknowns, of which the genetic test results would be one more puzzle piece. The expense of fertility testing/treatment was mentioned by both spouses, though more notably by husbands.</p> <p><u>Discussion:</u> The introduction of a possible genetic cause of infertility, with additional potential health consequences for future biological children, caused women to re-think their quest for pregnancy. In contrast, the genetic test was viewed as an additional source of information for their husbands as opposed to raising concern regarding potential reproductive ramifications.</p> | |
| 35 | <p>Chris Ghaemmaghami Characteristics of repeat emergency department users at a university medical center: frequent emergency department utilization is associated with higher rates of 30-day inpatient readmission</p> <p><u>STUDY OBJECTIVE:</u> Repeat emergency department (ED) users are common in academic and community hospitals alike, We conducted this study to characterize repeat ED users, according to frequency of repeat encounters.</p> <p><u>METHODS:</u> We performed a retrospective analysis of all ED visits over a 6 month period using an electronic database. Repeat ED users (REDUs) were defined as having 2 or more ED visits within the study period. We categorized patients as low REDUs (2-3 visits), moderate REDUs (4-9 visits) and high REDUs (> 9 visits). Comparisons were made to identify differences between REDUs and non-REDUs according to several demographic, medical and visit-related characteristics. Admission and 30-day readmission rates were calculated. Statistical analysis was performed using Chi-Square tests for categorical data and Fisher's exact test for small sample sizes as needed. Continuous data were analyzed using one way ANOVA and Student's t-tests.</p> <p><u>RESULTS:</u> REDUs accounted for 19.7% of all individual ED patients and 39.7% of visits. Low REDUs accounted for 28.9% of visits averaging 2.2 visits per patient, moderate REDUs accounted for 8.9% of visits averaging 4.9 visits per patient and high REDUs accounted for 1.9% of visits averaging 17 visits per patient. REDUs were more likely to be African American, living within close proximity to the hospital, publically insured, indigent and chronically ill. High REDUs were more likely to receive Medicare coverage (42.9%) and had significantly greater odds of having psychiatric comorbidities. Of note, low and moderate REDUs demonstrated no significant difference in the rate of inpatient admission per visit relative to that of non-REDUs (14.2%, 14.9% and 15.1% of ED visits, respectively), while high REDUs had significantly lower admission rates per visit (4.6%, $p < 0.001$). When admitted, all REDU groups demonstrated significantly higher rates of 30-day readmission (low- 25.8%, moderate- 42.1% and high- 68.2% of inpatient visits, p values < 0.05) in comparison to non-REDUs (6.7%). High REDUs had significantly shorter average lengths of stay (3.86 days, $p < 0.05$) compared with non-REDUs at 6.06 days.</p> <p><u>CONCLUSION:</u> REDUs tend to have more chronic illness, greater numbers of comorbidities and higher 2-year mortality than non-REDUs. Admission rates by visit were similar for all categories except for high REDUs, indicating that ED visits by low to moderate REDUs are justified as necessary. While high REDUs incur fewer and shorter inpatient admissions, they exhibit the highest rates of 30-day readmission. Federal programs designed to penalize providers for 30-day readmissions may be unreasonable for all patient populations.</p> | Ednam |
| 36 | <p>Jay W. Fox Insights in Dense Breast Carcinogenesis by Stromal Proteomics</p> <p>There is consensus that stroma plays a role in carcinogenesis and metastasis however the molecular details of this are still unclear. Interestingly although women with dense breasts, as visualized by mammography, are 4 fold more likely to develop breast cancer little is known at the molecular level as to what differences</p> | Ednam |

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| | are present between normal and dense breast stroma. We have investigated this by performing laser microdissection of stromal tissue from normal, dense and cancerous breast stroma to characterize their proteomes and analyze for differences which may play a role in carcinogenesis and metastasis. Our results suggest stromal makers for these various tissues and provide insight into potential mechanisms for carcinogenesis in these tissues. | |
| 37 | <p>John S. Lazo Disruption of the PI3K/mTOR pathway abrogates ionizing radiation-induced cell death</p> <p>Ionizing radiation induces genotoxic stress that triggers adaptive cellular responses, such as the phosphoinositide-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTor) pathways. Among the most important cells affected are the pluripotent populations required for cell replenishment. Effective and safe therapies are lacking to abrogate the lethal effects of an accidental or intentional public exposure to ionizing radiation. A computational analysis of an unbiased phenotypic screen with a library of small interfering RNA library targeting druggable genes implicated the PI3K/mTor pathway in the death of pluripotent NCCIT cells after ionizing radiation. Treatment of NCCIT cells with the prototype benzopyranone PI3K inhibitor LY294002 and the synthetic viridin EMF388-021 ((11-hydroxy-4-(methoxymethyl)-dimethyl-2,7,10-trioxo-1-(pyrrolidin-1-ylmethylene)-dodecahydroindeno[4,5-h]isochromen-5-yl acetate) PI3K inhibitor after 4 Gy ionizing radiation abrogated apoptosis. Moreover, administration of a single intraperitoneal dose of LY294002 (30 mg/kg) 4 or 24 h or EMF388-021 4 h after a lethal 9.25 Gy dose of ionizing radiation to mice significantly enhanced in vivo survival. Treatment of pluripotent NCCIT cells with rapamycin, everolimus and torin1, which are potent inhibitors of mTor, a proximal PI3K effector, also mitigated radiation-induced apoptosis. Both PI3K and mTOR inhibitors blocked NCCIT cell progression into S phase and stimulated an autophagic response, which could reduce radiation-induced death. This study implicates the PI3K/mTor pathway in the human radiation response and provides pharmacologically attractive mitigation targets.</p> | Ednam |
| 38 | <p>John S. Lazo Targeted deletion of the metastasis-associated phosphatase Ptp4a3 (PRL-3) suppresses murine colon cancer</p> <p><i>Ptp4a3</i> (commonly known as PRL-3) is an enigmatic member of the <i>Ptp4a</i> family of prenylated protein tyrosine phosphatases that are highly expressed in many human cancers. Despite strong correlations with tumor metastasis and poor patient prognosis, there is very limited understanding of this gene family's role in malignancy. Therefore, we created a gene targeted murine knockout model for <i>Ptp4a3</i>, the most widely studied <i>Ptp4a</i> family member. Mice deficient for <i>Ptp4a3</i> were grossly normal. Fewer homozygous-null males were observed at weaning, however, and they maintained a decreased body mass. Although <i>Ptp4a3</i> is normally associated with late-stage cancer and metastasis, we observed increased <i>Ptp4a3</i> expression in the colon of wildtype mice immediately following treatment with the carcinogen azoxymethane. To investigate the role of <i>Ptp4a3</i> in malignancy, we used the most commonly studied murine colitis-associated colon cancer model. Wildtype mice treated with azoxymethane and dextran sodium sulfate developed approximately 7-10 tumors per mouse in the distal colon. The resulting tumor tissue had 4-fold more <i>Ptp4a3</i> mRNA relative to normal colon epithelium and increased PTP4A3 protein. <i>Ptp4a3</i>-null mice developed 50% fewer colon tumors than wildtype mice after exposure to azoxymethane and dextran sodium sulfate. Tumors from the <i>Ptp4a3</i>-null mice had elevated levels of both IGF1Rβ and c-MYC compared to tumors replete with <i>Ptp4a3</i>, suggesting an enhanced cell signaling pathway engagement in the absence of the phosphatase. These results provide the first definitive evidence implicating <i>Ptp4a3</i> in colon tumorigenesis and highlight the potential value of the phosphatase as a therapeutic target for early stage malignant disease.</p> | Ednam |
| 39 | Amandeep Bajwa | Ednam |

| Poster | Presenter, title, abstract | Room |
|--------|--|-------|
| | <p>Cell-based therapy with S1P3 deficient dendritic cells induces prolongation of heart allograft survival and protection from kidney ischemic-reperfusion injury</p> <p>The plasticity of dendritic cells (DCs) permits phenotypic modulation <i>ex-vivo</i> by gene expression or pharmacological agents and these DCs exert their <i>in-vivo</i> therapeutic immunosuppressive effects through direct interactions with T-cells by either deleting or causing anergy. Sphingosine 1-phosphate (S1P), a sphingolipid that is the natural ligand for five G-protein coupled receptors (S1P1-5Rs) and S1PR agonists reduced kidney ischemia-reperfusion injury (IRI) in mice. Blocking S1P3 on DCs exert immunosuppressive properties. We tested the ability of S1pr3^{-/-} DCs to suppress kidney ischemia reperfusion injury (IRI) and acute rejection in allogeneic heterotopic heart transplantation (tx). Bone marrow derived DCs from B6 WT (B6DC) and B6 S1pr3^{-/-} (3KO B6DCs) mice were adoptively transferred into Balb/c mice two days prior to kidney IRI and seven days prior to heart tx (B6 heart→Balb/c). Naïve Balb/c mice (no DC injection) had significant rise in plasma creatinine (PCr; mg/dl) compared to sham operated mice (1.2±0.17 and 0.2±0.004, p≤0.01). However, 3KO B6DCs transferred into Balb/c mice (3KO B6DC→ Balb/c) were significantly protected from kidney IRI with PCr of 0.3±0.07, p≤0.01. 3KO B6DCs→ Balb/c had significantly higher Treg and less CD4 numbers compared to naïve Balb/c mice (no DC injection) and B6DC→Balb/c mice. The protective phenotype of 3KO B6DCs→Balb/c mice requires the recipient Balb/c mouse to have a spleen and presence of T and B cells; splenectomized (Splnx) Balb/c mice or use of Rag1KO rendered 3KO B6DCs ineffective in attenuating IRI. Furthermore, 3KO B6DC→Balb/c prior to heart transplantation results in better graft function with less infiltration of T cells and innate immune cells compared to no cells or WT DCs injected mice. We therefore conclude that adoptive transfer of 3KO B6DCs attenuates kidney IRI and better graft function (stronger heart beat at day 12) through interaction with splenocytes and induction of Tregs (CD4⁺FoxP3⁺).</p> | |
| 40 | <p>Weibin Shi Identification of atherosclerosis susceptibility genes acting at the level of the arterial wall</p> <p>Arterial wall inflammation is the central feature of atherosclerotic cardiovascular disease, but there are no effective medicines available to intervene the inflammatory process due to lack of appropriate targets. We have demonstrated that genetic factors acting at the level of the arterial wall play a crucial role in regulation of atherogenesis susceptibility in mouse models. When fed an atherogenic diet or deficient in apolipoprotein E (apoE^{-/-}), C57BL/6 (B6) mice develop much larger atherosclerotic lesions than C3H mice. We have found that vascular wall cells of B6 exhibit a dramatic induction of proinflammatory cytokines in response to oxidized LDL, whereas cells of C3H show little induction. Endothelial responses to oxidized LDL cosegregate with atherosclerotic lesion size in a set of recombinant inbred strains derived from the two strains. In an intercross between B6.apoE^{-/-} and C3H.apoE^{-/-} mice, we identified a significant atherosclerosis susceptibility locus, named Ath29, on chromosome 9. This locus was subsequently confirmed in a congenic line encompassing the C3H resistant allele. Microarray analysis of gene expression in the aorta of the congenic strain, as well as the two parental strains, revealed that genes involved in calcium signaling are implicated in control of atherosclerosis susceptibility. Rcn2, encoding a 55 kDa ER Ca²⁺-binding protein, is a promising candidate gene for Ath29. Multiple SNPs between B6 and C3H were found within and upstream the Rcn2 gene with one SNP falling within the cAMP response element. Rcn2 is expressed in atherosclerotic lesions. Knockdown with specific siRNAs uncovered a crucial role for Rcn2 in regulating both baseline and oxidized lipid-induced cytokine expression in endothelial cells. As a key regulator in the pathway of oxidized LDL-induced cytokine production, Rcn2 appears to be an appropriate target for pharmacological interventions of atherosclerosis.</p> | Ednam |
| 41 | Tarek Abbas | Ednam |

| Poster | Presenter, title, abstract | Room |
|--------|---|-------|
| | <p>CRL1-FBXO11 promotes Cdt2 ubiquitylation and degradation and regulates Pr-Set7/Set8-mediated cellular migration</p> <p>The Cul4-Cdt2 E3 ubiquitin ligase is a master regulator of cell cycle progression and genome stability. Despite its central role in the degradation of many cell-cycle regulators, e.g. Cdt1, p21 and Pr-Set7/Set8, little is known about the regulation of its activity. We report that Cdt2 is autoubiquitylated by the CRL4A E3 ubiquitin ligase. Cdt2 is additionally polyubiquitylated and degraded by Cul1-FBXO11. CRL1-FBXO11-mediated degradation of Cdt2 stabilizes p21 and Set8, and this is important during the response to TGF-beta, with the Set8 induction being important for turning off the activation of Smad2. The migration of epithelial cells is also stimulated by CRL1FBXO11-mediated downregulation of Cdt2 and the consequent stabilization of Set8. This is a novel example of cross-regulation between specific cullin 4 and cullin 1 E3 ubiquitin ligases and highlights the role of ubiquitylation in regulating cellular responses to TGF-beta and the migration of epithelial cells.</p> | |
| 42 | <p>Carol Gilchrist Entamoeba diversity in children who live in the urban slum of Mirpur, Bangladesh</p> <p>Multilocus sequence typing (MLST) of 16 loci were used to characterize <i>E. histolytica</i> isolates from children in the study cohort. <i>E. histolytica</i> does not appear to exist in a few main lineages and even in a population from a single geographic location, the majority of the individual parasites showed unique SNP genotypes. Despite this variability, two SNPs (SNPs 2725C/T & 2730A/G) within the cyclin-2 gene in one locus (AmoebaDB ID EHI_080100; XM_001914351) were associated with invasive amebiasis.</p> <p>EHI_080100 (cyclin-2) is present on a short region of contiguous DNA in the <i>E. histolytica</i> HM-1:IMSS genome assembly that could not be assembled into a larger contiguous DNA segment or sequence scaffold (DS571720). No sequences equivalent to the DNA within the <i>E. histolytica</i> DS571720 contig have been identified in the non-pathogenic <i>E. dispar</i> species.</p> <p>A longitudinal study of enteric pathogens infecting children who live in the urban slum of Mirpur, Bangladesh is ongoing and provides us with an opportunity to examine the genetic variation of this parasite in association with nother risk factors for amebiasis. Studies are ongoing to use MLST to analyze the diversity of <i>Entamoeba</i> in this sample set.</p> | Ednam |
| 43 | <p>Rahul Sharma Organ-specific inflammation: new mechanisms and therapeutic reagents</p> <p>The Foxp3-bearing regulatory T-cells (Treg) are major regulators of tolerance and their dysfunction triggers autoimmunity affecting multiple-organ systems. Mice (Scurfy or Sf) and humans (IPEX) with mutations in Foxp3 lack functional Tregs and die in infancy due to multi-organ inflammation. Interleukin-2 is important for Treg function and survival as IL-2 deficient mice (IL2KO) have reduced Tregs and they die early with multi-organ inflammation. We showed that in addition to its role in Treg homeostasis, IL-2 positively regulates the differentiation of T-helper type 2 cells (Th2) and allergic inflammation in skin and lungs. Importantly, IL-2 - regulated Th2 response protects against Th1 mediated inflammation in pancreas, salivary glands and liver. Further, IL-2 negatively regulates the differentiation of T-follicular helper cells (Tfh), which promote class-switch recombination and plasma cell differentiation for production of high-affinity autoantibodies. IL-2 regulates the Tfh in cis via STAT5-Blimp1-Bcl6 axis, but also in trans via Th2 cells, which suppress the Th1 cells to Tfh cells transition and their subsequent recruitment to pancreas, salivary glands and liver. The recently discovered cytokine IL-33 also acts as an alarmin and is important for the induction of the Th2 response. We found that the Treg cells as well as the Th2 cells highly express the receptor for IL-33 and that IL-2 upregulates the expression of IL-33 receptor on the CD4 T-cells. Based on these studies we have developed a novel bi-functional reagent bearing the activities of IL-2 and IL-33 (termed IL233), which not only will boost Treg and Th2 homeostasis, but will also suppress Tfh development and the Th1-mediated inflammation.</p> | Ednam |

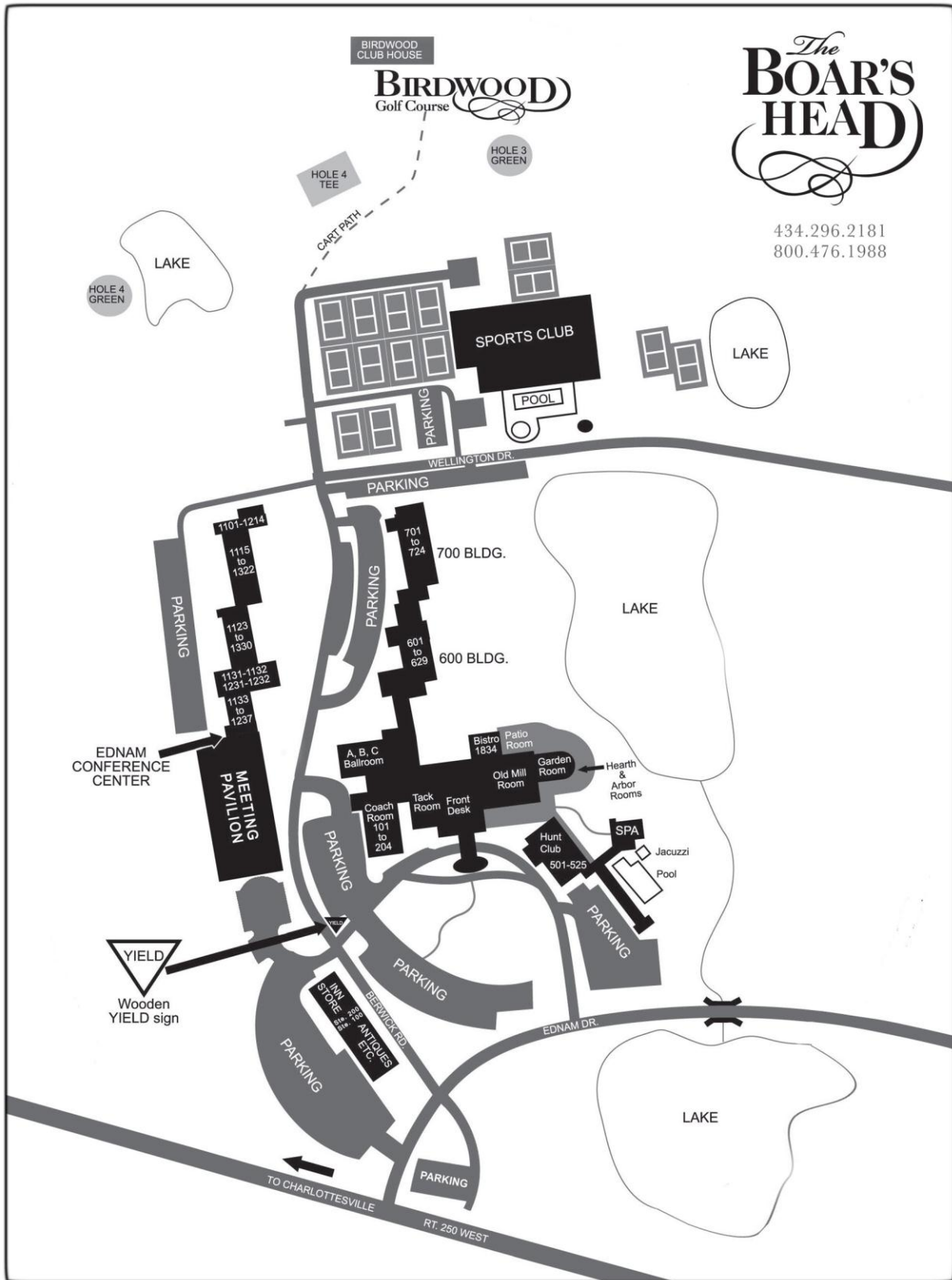
| Poster | Presenter, title, abstract | Room |
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| | <p>Preliminary studies show that pretreatment with the novel reagent is effective in chronic inflammatory diseases by protecting NOD mice against hyperglycemia. In a model of acute inflammation, IL233 pretreatment also protected mice against ischemia-reperfusion injury. The IL233 has a potential to be used as a therapeutic agent against autoimmune and inflammatory diseases by targeting multiple pathways.</p> | |
| 44 | <p>Noelle Dwyer The vertebrate-specific Kinesin-6, Kif20B, is required for cytokinesis of polarized cortical progenitors and normal cerebral cortex size During animal cell cytokinesis, the contractile furrow cleaves the cell and compacts the microtubules of the central spindle, forming the midbody. The midbody mediates abscission of the daughter cells by recruiting many factors including Kinesin-6. The mammalian Kinesin-6 family consists of the more conserved and well-studied members MKLP1 and MKLP2, and the less known vertebrate-specific member KIF20B. In mammalian neuroepithelial progenitors, the cytokinetic furrow ingresses from basal to apical, and the midbody forms at the apical surface. This polarized cytokinesis is not well understood. The mouse mutant, magoo, isolated in a prior forward genetic screen, has a small thin cerebral cortex. We show that the causative mutation is in the KIF20B gene. By in situ hybridization, KIF20B message is most strongly expressed in germinal zones of the developing nervous system. Immunostaining reveals that KIF20B protein localizes to midbodies of control progenitor cells, but is undetectable in magoo mutant cells. Mitotic and S-phase indices are similar in control and mutant cortical progenitors. Cytokinetic furrows and midbodies form in mutant progenitors, but the number and positioning of midbodies at the apical membrane is abnormal. Surprisingly, binucleate cells are not increased in magoo mutant brains, but apoptosis is increased, suggesting that failures in abscission of polarized cortical progenitors result in apoptosis rather than daughter re-fusion and binucleation. We conclude that KIF20B is required for proper abscission of polarized cerebral cortical progenitors, and has a critical role in normal cerebral cortex growth.</p> | Ednam |
| 45 | <p>Stefan Bekiranov Chromatin-mediated feedback loops control the epithelial-mesenchymal transition The epithelial-mesenchymal transition (EMT) is a cellular de-differentiation process that has been implicated in cancer progression and metastasis. Increasing evidence suggests that EMT is regulated and established by epigenetic reprogramming, however a systems-level mechanism describing how chromatin remodeling contributes to the phenotypic switch is not known. We have generated genome-wide maps of 16 histone modifications and 2 variants in both the epithelial and mesenchymal states and quantified patterns of epigenetic changes at gene and enhancer loci. Clusters of these patterns reveal that EMT-related genes and their proximal enhancers are regulated through coordinated patterns of chromatin activation and repression at both gene and enhancer loci. At the cellular level, the remodeling of gene loci translates into a modular protein interaction network that integrates EMT-related signaling. Moreover, differentially activated or repressed enhancers are associated with two nonoverlapping sets of transcription factors (TFs). We find chromatin-mediated activation of regulatory feedback loops involving NF-κB and AP-1, and analogous repression of MYC feedback.</p> | Ednam |
| 46 | <p>James W. Mandell Proteomic Identification of Mammalian Synaptic Caspase Substrates The dismantling and elimination of excess neurons and their connections (pruning) is essential for normal brain development and is thought to be aberrantly reactivated in some neurodegenerative diseases. A growing body of evidence implicates caspase-mediated apoptotic cascades in the dysfunction and death of neurons in neurodegenerative disorders such as Alzheimer's, Parkinson, and Huntington's diseases. It is the cleaved caspase substrates that actually perform the molecular functions leading to synapse elimination, yet the identities of these</p> | Ednam |

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| | <p>substrates, their cleavage sites, and the functional consequences of cleavage are largely unknown. Among the important neuronal proteins known to undergo functionally relevant caspase-mediated cleavage include tau, amyloid precursor protein, and huntingtin. These are likely to represent only the tip of the iceberg. An important gap in our knowledge is a comprehensive catalog of synapse-enriched caspase targets. Traditional biochemical approaches have limited utility in identifying cleavage events in complex biological samples and have revealed only a small number of neuronal caspase targets. We initiated a state-of-the-art proteomics approach to enable the first global analysis of caspase-mediated cleavage events in mammalian synapses. The guiding hypothesis for this project is that synapse elimination requires that a selected subset of synaptic proteins is targeted for caspase-mediated cleavage, leading loss- or gain-of-function important for inactivation of synaptic transmission and for efficient and non-inflammatory disassembly and removal. Our initial experiments, utilizing a neonatal mouse model of ethanol-induced neuronal apoptosis and synapse loss, revealed approximately 90-100 putative synapse-enriched proteolytic targets. The results of this work will direct future mechanistic studies on caspase-cleavage in synaptic pruning and elimination, and may lead to the discovery of novel serum or cerebrospinal fluid biomarkers to report synaptic loss in human neurological disorders.</p> | |
| 47 | <p>Valeria Mas MicroRNAs as Biomarkers in Solid Organ Transplantation Important progress has been made in improving short-term outcomes in solid organ transplantation. However, long-term outcomes have not improved during the last decades. There is a critical need for biomarkers of donor quality, early diagnosis of graft injury and treatment response. MicroRNAs (miRNAs) are a class of small single-stranded noncoding RNAs that function through translational repression of specific target mRNAs. MiRNA expression has been associated with different diseases and physiological conditions. Moreover, miRNAs have been detected in different biological fluids and these circulating miRNAs can distinguish diseased individuals from healthy controls. The noninvasive nature of circulating miRNA detection, their disease specificity and the availability of accurate techniques for detecting and monitoring these molecules has encouraged a pursuit of miRNA biomarker research and the evaluation of specific applications in the transplant field. miRNA expression might develop as excellent biomarkers of allograft injury and function. We will present our recently accomplishments in miRNA studies as biomarkers in progression to chronic allograft dysfunction and ischemia reperfusion injury.</p> | Ednam |
| 48 | <p>Randall Moorman Predictive informatics monitoring at the bedside Our goal is to develop predictive monitoring for early diagnosis of subacute, potentially catastrophic illness. To date, our focus has been on premature infants in an intensive care unit. The clinical problem that we first addressed is neonatal sepsis, a bacterial infection of the bloodstream in premature newborn infants in the intensive care unit. This illness is common and adds greatly to morbidity and mortality of these fragile patients, and is difficult to diagnose in its early and most treatable stages. We reasoned that continuous monitoring of a sensitive physiological measure like heart rate variability might show changes before obvious signs of a critical illness so advanced that therapy would not help. We began by inspecting heart rate records over prolonged periods in infants at risk of sepsis. We found obvious changes in the heart rate characteristics of septic infants even before they were clinically ill, with reduced variability and transient decelerations similar to the findings in fetal distress. Since there were no measures available to detect these findings, we developed new mathematical techniques of sample entropy and sample asymmetry. We did clinical studies to develop predictive multivariate statistical models based on our new measures, and we validated them at a second medical center. We recently completed a multicenter</p> | Ednam |

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| | <p>randomized clinical trial of 3000 very low birthweight infants into to test the hypothesis that our monitoring system improves infants' outcomes. Indeed it does - monitored infants had a more than 20% reduction in mortality.</p> <p>We intend to carry these ideas into other clinical settings, especially hospital units in which continuous monitoring is already the standard of practice such as the MICU and SICU.</p> | |
| 49 | <p>Ayotunde Dokun The Role of ADAM12 as a Modifier of Outcomes in Experimental PAD <u>Background:</u> PAD results from atherosclerotic occlusion in the arteries of the lower extremities and PAD has a prevalence of 8-12 million in the US. There are two major classifications of PAD: intermittent claudication, which is pain with exercise and critical limb ischemia, which is pain at rest, and may be associated with ulcers or gangrene. Critical limb ischemia is associated with a 6 month amputation rate of 20-45% and an annual mortality as high as 20%. There is emerging evidence that genetic factors and the presence of diabetes strongly affect whether an individual will develop critical limb ischemia when they have PAD. Nevertheless, specific genes that contribute to this outcome are not known. In a pre-clinical model of PAD, we previously identified a genetic locus termed LSq-1 which when present (C57Bl/6 mice) is associated with good blood flow recovery and tissue survival and its absence (Balb/c mice) is associated with poor blood flow recovery and tissue death. Using haplotype mapping we have further narrowed this locus and q-RTPCR of genes within this locus has identified a number of candidate genes including ADAM12.</p> <p>ADAM12 is a membrane-bound protease expressed during development, in remodeling tissues and members of the ADAM family of proteins have been linked to adaptive blood vessel growth.</p> <p><u>Hypothesis:</u> ADAM12 is sufficient to improve outcomes in a preclinical model of PAD and its effects occur via modulation of endothelial cells.</p> <p><u>Results:</u> Our analysis showed ADAM12 mRNA expression is up-regulated >10 fold in ischemic hind limb muscles compared to non-ischemic muscles and expressed at about 50% higher levels in ischemic muscles from C57BL/6 mice which displays good recovery compared to the Balbc/c mice that has poor recovery. Moreover, increased expression of ADAM12 in mouse hind limb muscles by gene transfer significantly improved perfusion recovery in experimental PAD (change in perfusion = 81%±6.57 vs 40%±7.59 p=0.001 at week 3 post PAD induction). Analysis of ADAM12 mRNA expression in ischemic muscles showed its expression is up-regulated primarily in endothelial cells. Over expression of ADAM12 in endothelial cells increased cell proliferation and survival in simulated ischemia. "Knock down" of ADAM12 expression by shRNA impaired endothelial cell proliferation and increased apoptosis in simulated ischemia.</p> <p><u>Conclusion:</u> ADAM12 is a gene within LSq-1 that mediates PAD outcomes via modulation of endothelial cell proliferation and survival.</p> | Ednam |
| 50 | <p>Paul S. Hoffman Amixicile, a Novel Inhibitor of Pyruvate:Ferredoxin Oxidoreductase, Shows Efficacy against Clostridium difficile and Helicobacter pylori in Mouse Infection Models <i>Clostridium difficile</i> infection (CDI) is a serious diarrheal disease that often develops following prior antibiotic usage. One of the major problems with current therapies (oral vancomycin and metronidazole) is the high rate of recurrence. <i>Helicobacter pylori</i> establishes lifelong infections of the gastric mucosa of humans, causing gastritis, stomach ulcers and is a risk factor for gastric cancer. Treatment of <i>H. pylori</i> infections requires triple and quadruple therapies and drug resistance is a growing challenge. These pathogens along with all strictly anaerobic bacteria, parasites and <i>Campylobacter jejuni</i> utilize pyruvate: ferredoxin oxidoreductase (PFOR) instead of pyruvate dehydrogenase in their central metabolism. We have developed a novel therapeutic from the scaffold of nitazoxanide (Amixicile) that out competes pyruvate for binding to the thymine pyrophosphate vitamin cofactor of</p> | Ednam |

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| | <p>PFOR. Amoxicillin is water soluble, absorbed and reaches therapeutic concentrations in serum, is not metabolized by liver microsomes and is well tolerated in mice and rats. In an optimized mouse model, amoxicillin showed equivalence to vancomycin and fidaxomicin at day 5 and significantly greater survival produced by amoxicillin than by the other drugs on day 12. Recurrence of CDI was common for mice treated with vancomycin or fidaxomicin, but not with mice receiving amoxicillin. These results suggest that gut repopulation with beneficial (non-PFOR) bacteria, considered essential for protection against CDI, rebounds much sooner with amoxicillin therapy than with vancomycin or fidaxomicin. In the H. pylori mouse model, amoxicillin was nearly as effective as metronidazole, the gold standard. If the mouse model is indeed predictive of human CDI and H. pylori diseases, then amoxicillin, a novel PFOR inhibitor with no documented drug resistance, appears to be a very promising new antimicrobial.</p> | |
| 51 | <p>Lukas Tamm Center for Membrane Biology at the University of Virginia The UVa Center for Membrane Biology comprises faculty from six Departments and three Schools of the University of Virginia. The assembled faculty share common research and teaching interests to achieve a deeper understanding of how biological membranes function as barriers of individual cells, organisms, and organelles. Many diseases are rooted in disorders of membrane functions. It is the goal of the Center to discover and teach students membrane-associated biological processes and to translate basic discoveries into cures for numerous diseases. Basic research emanating from the Center is therefore intimately relevant to understanding molecular mechanisms of disease including cancer, diabetes, hypertension, atherosclerosis, as well as infectious, neurological, and neurodegenerative diseases.</p> | Ednam |
| 52 | <p>Jay Brown Replication of Herpes Simplex Virus: Egress of Progeny Virus at Specialized Cell Membrane Sites In the final stages of the HSV-1 life cycle, a viral nucleocapsid buds into a vesicle of TGN/endosome origin acquiring an envelope and an outer vesicular membrane. The virus-containing vesicle then traffics to the plasma membrane where it fuses, exposing an enveloped virion. Here we describe our observations on HSV-1 egress as it occurs in non-polarized cells. Infected Vero cells were examined by electron, confocal, and TIRF microscopy. The results revealed that HSV-1 was released at specific pocket-like areas of the plasma membrane. These were found along the substrate-adherent surface and at cell-cell adherent contacts. Both the membrane composition and cytoskeletal structure of egress sites were found to be modified by infection. The plasma membrane at the virion release sites was heavily enriched in viral glycoproteins. Glycoprotein-rich areas formed independently from virion trafficking as confirmed by use of a UL25 mutant with a defect in capsid nuclear egress. Small glycoprotein patches formed early in infection and virus became associated with these areas at later timepoints. Depolymerization of the cytoskeleton indicated that microtubules and actin were both important for trafficking of virions and glycoproteins to release sites. In addition, the actin cytoskeleton was found to be necessary for maintaining the integrity of egress sites. When actin was depolymerized, the glycoprotein concentrations dispersed across the membrane as did the surface-associated virus. Lastly, cells infected with gE deletion mutants formed glycoprotein patches that were significantly reduced in size, although the total amount of virus released at these sites was increased. The results of this study are interpreted to indicate that egress of HSV-1 in Vero cells is directed to virally induced, specialized egress sites that form along specific areas of the cell membrane.</p> | Ednam |
| 53 | <p>Zhen Yan Muscle-derived extracellular superoxide dismutase in protection against multiple organ dysfunction syndrome in mice Critically ill patients with sepsis, trauma or other serious medical conditions often</p> | Ednam |

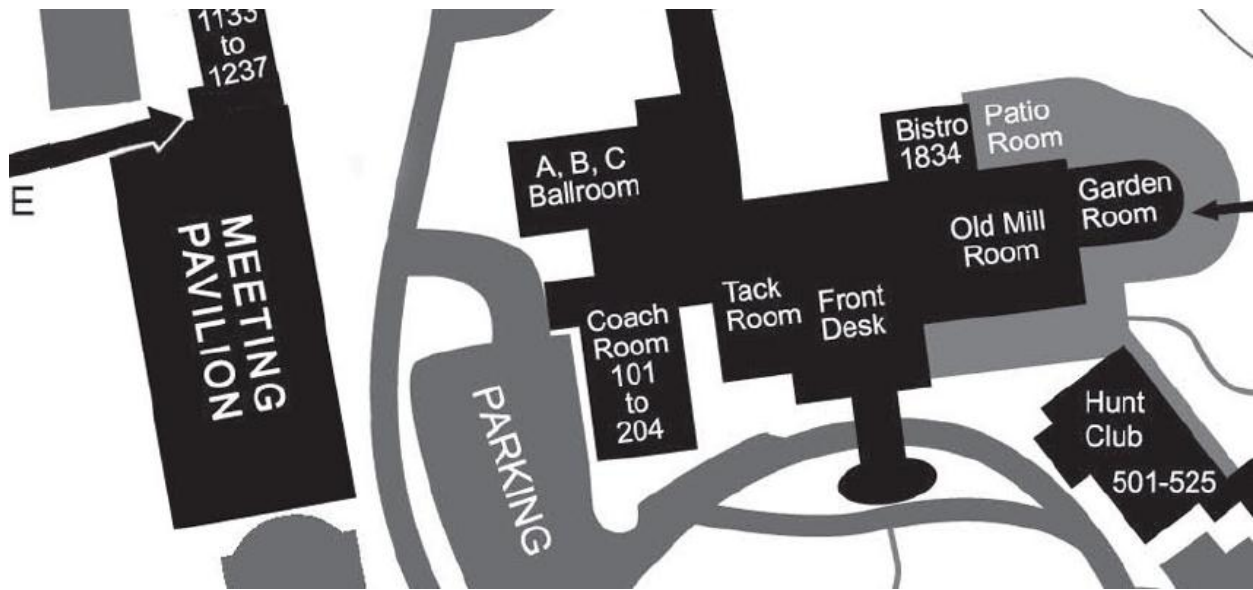
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| | <p>develop multiple organ dysfunction syndrome (MODS), a major cause of death in the intensive care unit with 30-80% mortality rate. Emerging evidence suggests that oxidative damage/activation of the endothelium of vital organ vasculatures is a key, early step of a cascade of cellular and signaling events in the etiology of MODS. We have generated muscle-specific extracellular superoxide dismutase (EcSOD) transgenic mice (TG) and found that overexpressed EcSOD redistributes to other peripheral tissues/organs through the circulation and enriches at the endothelium. Importantly, these TG mice are profoundly protected from endotoxemia (lipopolysaccharide (LPS) 20 mg/kg, i.p.)-induced MODS with significantly reduced mortality, oxidative stress, inflammation, and coagulation in the lung, kidney and other peripheral tissues. Heterochronic parabiosis between TG and wild type littermate (WT) mice with shared circulation and redistribution of EcSOD, conferred a significant protection to the WT mice, which was not found in isochronic parabiosis between WT mice. Finally, pre-incubation of cultured human coronary arterial endothelial cell (HCAEC) monolayer with serum from TG mice showed significantly attenuated vascular cell adhesion molecule 1 (VCAM-1) expression in response to tumor necrosis factor-α (TNF-α) treatment. These findings strongly support that muscle-derived EcSOD is sufficient to provide protection against MODS induced by endotoxemia at least partly by reducing endothelium damage/activation, provide proof-of-principle information about the feasibility of therapy for MODS by promoting EcSOD expression in skeletal muscle.</p> | |



The
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Map of the Boar's Head Inn
(Attendees may park in any lot pictured)



Detail of previous map, highlighting event meeting rooms:

Pavilion: dinner, poster, lunch & concurrent sessions

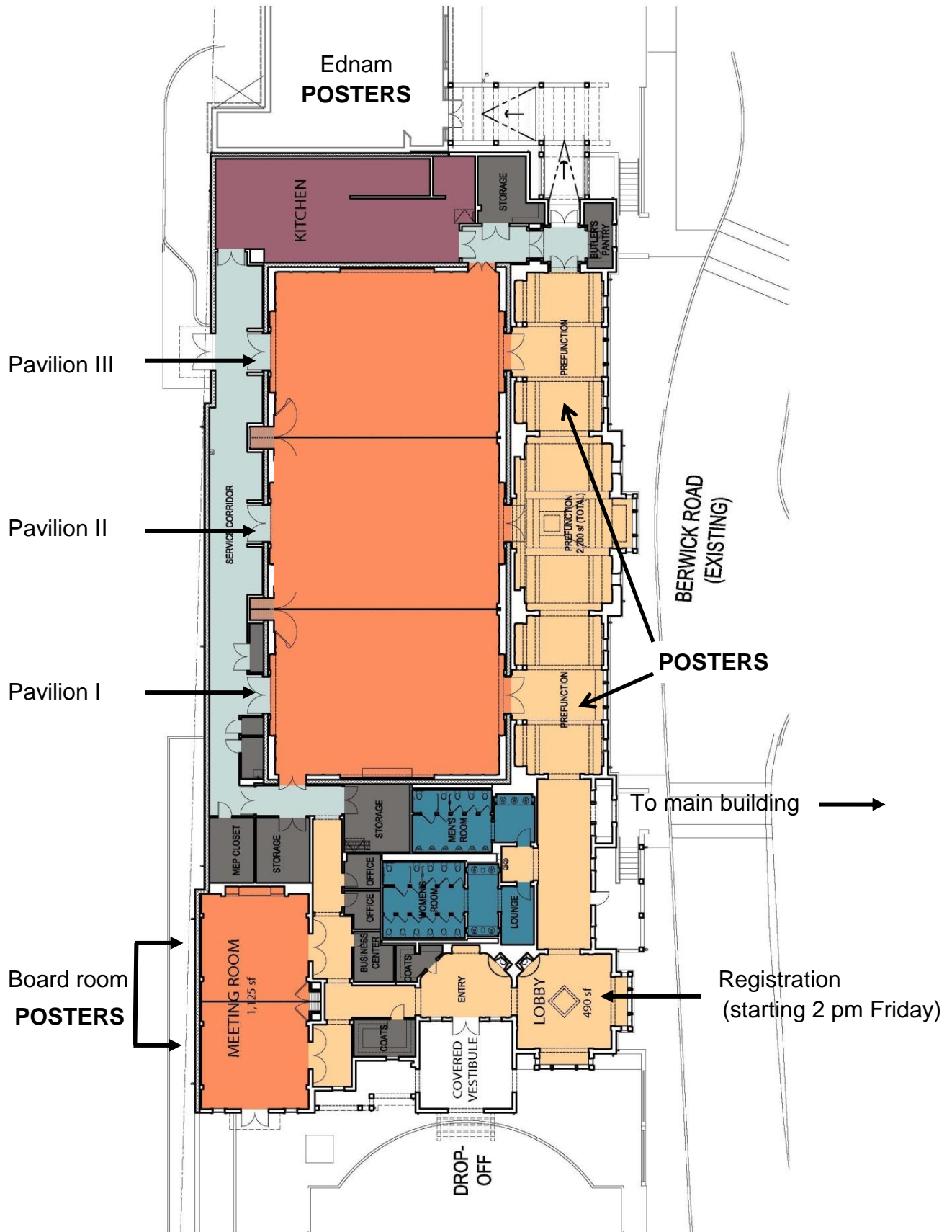
Ednam: poster sessions

Coach Room: lunch sessions

Ballroom: lunch sessions

“A,B,C:” lunch sessions (located above ballroom)

Old Mill, Garden, Patio Rooms: lunch sessions



Pavilion - layout
 University of Virginia School of Medicine
 2013 Faculty Research Retreat

Reminders from the Office for Research (OFR) and Office of Grants and Contracts (OGC)

Feedback on the retreat. Please help us to improve future research retreats by providing your feedback at <http://www.medicine.virginia.edu/research/offices/research/2013-faculty-research-retreat-feedback>:



Seminar calendar. The Health System calendar of events can be accessed at <http://www.healthsystem.virginia.edu/events/index.cfm?viewformat=week&viewtype=som&startdate=01%2F05%2F2012&searchstring=Search+Events&filterdepartment=2&filtereventtype=2> 3. Please ask your administrator to list upcoming seminars on that site, in order to broadcast them to all faculty.

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