NATIONAL STUDENT RESEARCH FORUM

50th ANNUAL MEETING
April 23 – April 25, 2009

Sponsored by:
The University of Texas Medical Branch
Galveston, Texas

Supported by a grant from the
AMA Foundation
# TABLE OF CONTENTS

American Medical Association Foundation ................................................................. 1
Support for the NSRF .................................................................................................... 3
President’s Welcome .................................................................................................... 4
Introduction and History ............................................................................................ 5
Co-Directors & Faculty Advisors .................................................................................. 6
Schedule of Events ....................................................................................................... 15
In Appreciation .......................................................................................................... 19
Judges and Reviewers ................................................................................................. 20
Excellence in Research Awards .................................................................................... 21
Determination of Awards ............................................................................................. 23
2009 Abreu Memorial Keynote Lecture Series ............................................................ 24

**Oral Presentations**

| Session A: Orthopedic Medicine and Surgery | 27 |
| Session B: Public Health and Medical Humanities | 28 |
| Session C: Biochemistry and Cell Biology | 29 |
| Session D: Microbiology and Immunology | 30 |
| Session E: Neuroscience | 31 |
| Session F: Oncology and Cancer Cell Biology | 32 |

**Poster Presentations Session 1**

| Cardiology | 34 |
| Dermatology | 35 |
| Obstetrics and Gynecology | 36 |
| Orthopedic Medicine | 37 |
| Physiology | 38 |
| Public Health | 39 |
| Radiology | 40 |
| Surgery | 41 |

**Poster Presentations Session 2**

| Biochemistry | 42 |
| Cell Biology | 43 |
| Genetics | 44 |
| Immunology | 45 |
| Microbiology and Infectious Disease | 46 |
| Neuroscience | 47 |
| Oncology | 48 |
| Pathology | 49 |
| Pharmacology and Toxicology | 50 |

**Oral Abstracts** ......................................................................................................... 51-72
**Poster Abstracts** ...................................................................................................... 73-122
**Index of Participants** .............................................................................................. 117
The American Medical Association Foundation is proud to be a sponsor of the 2009 National and Regional Student Research Forums.

As the philanthropic arm of the American Medical Association (AMA), the AMA Foundation works to advance the health care of America through quality programs in medical education and public health:

**MEDICAL EDUCATION**
The AMA Foundation encourages the best and brightest physicians-in-training through research seed grants and scholarships. These programs support individuals just starting out in the medical field, offer professional development among budding researchers, and provide tuition assistance for medical school.

**PUBLIC HEALTH**
The AMA Foundation also funds public education initiatives and community service efforts across the country. These programs include distributing health literacy and patient safety resources, awarding mini-grants for grassroots public health projects, and supporting free clinics that provide medical care to the uninsured.

To apply for research grants and scholarships, visit [www.amafoundation.org](http://www.amafoundation.org)
Dr. Owen Garrick currently serves as treasurer of the American Medical Association (AMA) Foundation and was elected to its Board in 2004.

He is Chief Operating Officer and Director at HOV Clinical Research Inc. He is responsible for managing the Clinical Trials and Investigator Training business units, and oversees all financial, administrative, and legal aspects of the company.

Prior to HOV Clinical Research, Inc., Dr. Garrick was the Director of Corporate Strategy and Business Development at McKesson Corporation. He pursued vertical integration opportunities with generic drug manufacturers and upstream product development. He also developed and launched the company’s Drug Adherence Business focused on pharmaceutical and biotechnology manufacturers.

He also served as Executive Director and Co-Head of Mergers & Acquisitions at Novartis Pharmaceuticals. In this position, he led all global M&A activity up to $5 billion. He specifically oversaw small and medium size company acquisitions, hybrid equity/license right deals, mature product divestments, and venture investments in biotechnology companies.

Previously he spent four years at Goldman Sachs in New York, functioning as an investment advisor working with private healthcare companies as they sought to grow, raise capital, and perform initial public offerings.

Dr. Garrick earned his MD from the Yale School of Medicine and his MBA from the Wharton School of Business. He holds an AB in Psychology from Princeton University and continues to be an active alumnus, serving on the national fundraising board. He also serves on other boards and professional committees, including the New York Blood Center and the Sutter Healthcare System.

He is married to Dr. Jocelyn Garrick, an assistant professor of medicine at the University of California, San Francisco where she also practices emergency medicine.
Special Thank You to the
2009 National Student Research Forum Supporters

The awards presented at the 2008 National Student Research Forum are generously funded by many organizations, individuals and UTMB Department Chairs. We appreciate your continued support!

The primary sources of support for the operation of the Forum are the:

AMERICAN MEDICAL ASSOCIATION FOUNDATION

and

THE UNIVERSITY OF TEXAS MEDICAL BRANCH AT GALVESTON

UTMB encourages progress and excellence in medical education and research!

Clinical Research Education Office
Department of Anesthesiology
Department of Biochemistry and Molecular Biology
Department of Dermatology
Department of Internal Medicine
Department of Microbiology and Immunology
Department of Neuroscience and Cell Biology
Department of Obstetrics and Gynecology
Department of Pathology
Department of Pediatrics
Department of Pharmacology and Toxicology
Department of Preventive Medicine and Community Health
Department of Radiology
Department of Surgery
Graduate School of Biomedical Sciences
Institute for Human Infections and Immunity
John P. McGovern Academy of Oslerian Medicine
School of Medicine, Office of Student Affairs and Admissions
Sealy Center for Vaccine Development
Dear Forum Participants:

On behalf of the students, faculty and staff of The University of Texas Medical Branch, I am delighted to welcome you to the 50th Annual National Student Research Forum. This marvelous tradition celebrates 50 years of bringing together medical and graduate students from across the country and the world. The forum has grown from a small regional meeting to a nationally respected assembly of young scientists. Students have the opportunity to present their research, receive meaningful feedback and participate in scholarly discussion with peers and established scientists.

Dr. Orian S. Shirihai from Boston University School of Medicine and Dr. David Ferrick, Chief Scientific Officer from the Seahorse Bioscience are our keynote speakers. Dr. Shirihai will speak on Thursday, April 23rd and Dr. Ferrick on Friday, April 24th.

Every year, we look forward with great anticipation to this assembly and this year is extra special celebrating our community’s resiliency from Hurricane Ike. We hope you will take full advantage of the 2009 National Student Research Forum and will return to your home schools having gained both a valuable presentation experience and a renewed sense of camaraderie with your fellow scientists.

Welcome to Galveston!

Sincerely,

David L. Callender, MD, MBA, FACS  
President
INTRODUCTION AND HISTORY

BACKGROUND
The National Student Research Forum is organized and run by students for the discussion of student research papers in a scientific atmosphere. Originating in 1960 at the University of Texas Medical Branch in Galveston, the first Forum had participants from Texas, Louisiana, Arkansas, and Tennessee. Last year approximately 140 students from 50 medical schools and hospitals throughout the United States and Canada presented papers. The National Student Research Forum now affords young scientific investigators one of their major opportunities to participate in a scientific meeting and the 2009 Forum is expected to be represented in several major fields of medical research.

During the 1959-60 academic year, a small group of medical students involved in research approached Dr. James V. Warren, then-Chairman of the Department of Internal Medicine, for his help in setting up a forum for the presentation of their work. Supported by the Executive Committee of the Faculty of Medicine, Dr. Warren recruited both the James W. McLaughlin Committee, which supports research in infection and immunity, and the Galveston Chapter of Sigma Xi, which is dedicated to the encouragement of research, to help finance and organize the first Forum. That meeting was open to medical students in the southwestern United States and was held at the Hotel Galvez in March 1960. The success of the first effort led to yearly Forums organized, directed, and presented by students.

In 1963, Dr. Benedict E. Abreu, then Chairman of the Department of Pharmacology, became faculty advisor to the Research Forum. Dr. Abreu's goal was to have the Forum become national in scope, which would provide a much-needed opportunity for the presentation of research by students. By 1963, the Forum had already grown into a project too large for its two original supporters. Dr. Abreu persuaded Mead Johnson Laboratories to become a major supporter of the Forum, and by 1964, twenty-two drug companies were contributing, thanks to Dr. Abreu's active solicitation.

When Dr. Abreu died in January of 1965, the Forum sought administrative support from UTMB. Planning and management remained the responsibility of the students and, in 1968, representatives from the National Office of the Student American Medical Association agreed to officially designate the program the SAMA-UTMB National Student Research Forum. Sixty nine medical schools were represented in 1968, and the Forum continued to grow in size and diversity. In 1978, a truly national Forum was realized, with 135 papers presented in 17 sessions.

PURPOSE AND OBJECTIVES
The primary purpose of the National Student Research Forum, now in its forty-ninth year, is to provide a national scientific assembly, planned and managed by students for presentation of research by medical students, interns and residents, and graduate students in the health sciences. The Forum recognizes excellence in research by means of awards, based upon the judgement of a panel of medical scientists selected from the UTMB faculty. The Forum provides an opportunity for young health scientists to receive meaningful and pertinent discussion of their research efforts by their peers and by established scientists in an atmosphere encouraging the highest scientific standards. The leadership of the National Student Research Forum has encouraged and will continue to encourage the establishment of local and regional student research forums. The prize-winning papers from the local meetings are automatically accepted for presentation at the National Student Research Forum.
2009 50TH National Student Research Forum Co-Directors

Sarah Ziegler - Senior Co-Director
This is the second year that Sarah has been a Senior Co-Director of the NSRF. Sarah graduated from the University of Nevada in Las Vegas in 2003 with a B.S. degree in Biochemistry. She later received her M.S. degree from UNLV also in Biochemistry. Sarah came to the University of Texas Medical Branch with her husband and daughter in 2006. She is currently a third year student in the Department of Experimental Pathology. Her current research focus is on the pathogenesis of chikungunya virus in mice. She has presented her scientific research at many national conferences.

Sarah Castro – Co-Director
Sarah graduated magna cum laude from Wichita State University with a B.S. degree in Biology and minor in Chemistry. During her time at Wichita State, Sarah conducted research in an environmental microbiology lab where she investigated halophilic Archaea from the salt plains of Oklahoma. Sarah began her graduate education at UTMB in 2006. She is currently a third year student in the Department of Microbiology and Immunology. Sarah was awarded a NASA predoctoral fellowship and is conducting her doctoral research at NASA’s Johnson Space Center. Her research focuses on the effects of a low-shear environment in altering the characteristics of Staphylococcus aureus. This is Sarah’s second year serving as a co-director for the National Student Research Forum.
2009 50TH National Student Research Forum Co-Directors

Ashley Grant – Co-Director
Ashley graduated from the California Institute of Technology with a BS in Chemistry and Business Economics and Management. Ashley is a second year graduate student in the Experimental Pathology program at the University of Texas Medical Branch. Ashley is performing her dissertation research on viral hemorrhagic fevers under Dr. CJ Peters. Ashley is a Keck Viral Imaging Fellow and a Fogarty International Research Fellow. In her spare time, Ashley enjoys traveling, home improvement, playing sports, and cooking.

Sarah Hemauer – Co-Director
Sarah graduated from the University of Wisconsin-Madison in 2005 with a B.S. in Biology, where she studied cardiopulmonary interactions during exercise as an American Physiological Society Undergraduate Research Fellow. She came to the University of Texas Medical Branch in 2006, and is now in her third year of the M.D./Ph.D. program. Her doctoral research in the Department of Biochemistry & Molecular Biology focuses on the role of the placenta in fetal protection during high risk pregnancies, and was awarded the 2007 John Gibbons Medical Student Award from the American College of Obstetricians and Gynecologists as a result of her work. She has presented her research at the International Union of Physiological Sciences and the Society of Maternal-Fetal Medicine annual meetings.
Sharon Ho - Co-Director
Sharon Ho graduated cum laude from Rice University in 2007 with a B.A. in psychology. During her time at Rice, she was involved in cognitive psychology research, studying the development of reading expertise in children. Additionally, during her undergraduate years, Sharon conducted research on the regulation of embryonic stem cell function at Baylor College of Medicine in the Department of Molecular and Cellular Biology. Sharon is currently a second year medical student at UTMB. She is actively involved with the American Medical Women's Association and recently organized a charity ball which raised over five thousand dollars for a local charity.

Van Hoang – Co-Director
Van graduated from the University of Texas at Austin in 2007 with a degree in Biology. Throughout her undergraduate education, she was involved in multiple research projects, including an investigation on the signal transduction of anticancer therapeutics in small-cell lung cancer cells. As an undergraduate research fellow of the American Heart Association, she investigated transcriptional regulation of vascularization in the developing lung. Her more recent research interests include infectious diseases and molecular biology, specifically the replication, gene expression, and mechanisms of drug resistance of the influenza virus. She is currently a second-year medical student and working towards a Ph.D.
2009 50TH National Student Research Forum Co-Directors

Joseph R. Karam – Co-Director

Joseph R. Karam is a fourth year medical student at UTMB, and a returning co-director of the National Student Research Forum. After graduating from Trinity University in San Antonio in 2002 with a Bachelor of Science in Biochemistry and Molecular Biology, he worked in a research lab at Baylor College of Medicine investigating Crohn’s Disease. In 2003, he began graduate school at UTMB and earned a Master of Science in Pharmacology and Toxicology. Less than a week after defending his thesis, he began medical school at UTMB in 2005. During his medical education he has remained involved in various research projects ranging from the Department of Neuroscience where he investigated ALS, to the Department of Surgery, Division of Pediatrics where he is currently investigating Neuroblastoma. Following medical school, Joseph will begin his residency training in the field of General Surgery where he plans to remain involved in research and eventually pursue a career in Pediatric Surgery.

Nguyen Nguyen – Co-Director

Nguyen graduated from the University of Texas at Austin with a B.S. in neurobiology and a minor in computer science in 2006. During his time there, he was awarded a Junior Research Fellowship grant, which he used to study calcium gated potassium channels in Drosophila Melanogaster and their role in alcohol tolerance. He was also a physiology undergraduate fellow at UTHSC San Antonio, where he studied the electrophysiology of these potassium channels using patch clamping. Following his graduation from UT Austin and prior to entering medical school, he spent a year in Dr. Patricia Dahia’s lab at UTHSC San Antonio to study the genetics and molecular biology of the adrenal gland tumor pheochromocytoma. He is currently a second year medical student at UTMB with aspirations to improve the health status of his birth country Vietnam.
Linda Sousse - Co-Director

Linda graduated from Texas A&M University-Corpus Christi in 2004 with a B.S. degree in Chemistry and in Biology. She later received her M.B.A. degree from TAMU-CC in Business Administration. During her time at TAMU-CC, Linda conducted research in an environmental toxicology lab where she investigated nfi from bacterial samples in the Gulf of Mexico. Linda began her graduate education at UTMB in 2006. She is currently a third year student in the Department of Experimental Pathology. Her research focuses on the relationships between arginase, NOS, and ADMA to excess collagen deposition in inhalation injury. She has presented her research at the American Society of Anesthesiologists and the Federation of American Societies for Experimental Biology.

Katie Taylor - Co-Director

Katie graduated from Texas A&M University with a B.S. in Biomedical Science. After graduating she finished her high school teaching certification and taught 9th grade. Katie is a second year graduate student in the Experimental Pathology at the University of Texas Medical Branch. Her research focuses on the role of regulatory T cells in preventing viral encephalitis under Dr. Mark Estes and Dr. Slobodan Paessler. She is a recent recipient of a Department of Homeland Security (DHS) fellowship sponsored by a DHS Career Training Grant from the Foreign and Animal Zoonotic Disease Center.
Eric Vu – Co-Director

Eric graduated magna cum laude from Rice University in 2006 with a B.S. in Bioengineering and focus area in cellular/molecular engineering and biomechanics. During his time at Rice, he was involved in several research projects in molecular biology, radiology imaging, and orthopedics. In 2006, Eric completed a NASA funded design project for an orthopedic device designed to improve fracture healing. This patent-pending device was awarded top honors at NASA’s RASC-AL national design competition and subsequently presented at the American Institute of Aeronautics and Astronautics Space Conference and the BioHouston Orthopedic Medical Device Emerging Technology Showcase. This work has been presented with the McLucas Award for Study in Space Safety. Eric is currently a third year medical student at UTMB.
2009 Faculty Advisors

Judith F. Aronson M.D.
Judith F. Aronson, M.D. is currently Professor and Vice Chair for Education in the Department of Pathology at UTMB. She received her undergraduate education at Yale University and her M.D. degree from the University of North Carolina at Chapel Hill. She subsequently did residency training in Anatomic Pathology at the University of Washington, Seattle, and UTMB, followed by post-doctoral training in virology at the University of North Carolina. Her main interests are pathology and pathogenesis of infectious diseases, especially viral hemorrhagic fevers. She currently serves as Associate Director of the Experimental Pathology Core of the Galveston National Laboratory. She is active at UTMB in education of medical students, graduate students and pathology residents. She has received a number of teaching awards at UTMB and is an elected member of the Academy of Master Teachers. Since 2004, she has been a William Osler Scholar in the John P. McGovern of Oslerian Medicine at UTMB.

Randall L. Given, Ph.D.
Dr. Given is a native of Idaho and received his B.S. in Zoology from the University of Idaho in 1972. He earned his Ph.D. in Anatomy and Developmental Biology in 1978 from Washington University in St. Louis and worked as a postdoctoral fellow at the University of California at Davis and Oregon Health Sciences University in Portland, Oregon. In 1982, he moved to UTMB and is currently an Associate Professor of Neuroscience and Cell Biology. His research interests involve the implantation of the early embryo in the uterine endometrium and functional control of the invasion process including epithelial and connective changes and nitric oxide influence on vasculature. In addition, he is the course director for Molecules, Cells, and Tissues and a faculty member in the Gross Anatomy and Radiology course. He is also a member of the Cell Biology Graduate Program.
Jeffrey P. Rabek, Ph.D.

Dr. Rabek received a B.A. in Zoology from Drew University in Madison, New Jersey in 1971 and a Ph.D. in Biochemistry from Princeton University in 1976. He did postdoctoral work at Oak Ridge National Laboratory, Oak Ridge, Tennessee. Dr. Rabek is the Assistant Dean for Student Affairs and Admissions in the School of Medicine, an assistant professor in the Departments of Biochemistry and Molecular Biology and Family Medicine, and a Fellow in the Sealy Center for Aging at UTMB. Dr. Rabek’s major research interests lie in the control of the temporal and tissue-specific expression of specific genes during development and aging, and in response to stress. Control mechanisms acting at the level of the induction and regulation of gene transcription and messenger RNA translation are of particular interest. Dr. Rabek’s research interests also include a longitudinal study looking at protein markers and protein damage in tissue from muscles paralyzed after stroke, through functional recovery. Dr. Rabek has been particularly active in the educational mission of UTMB in both the Graduate School of Biomedical Sciences and the School of Medicine. He lectures in numerous graduate school courses and serves as a course director. In the medical school, he has served as co-director of the Molecules Cells and Tissues module, is a member of the Family Medicine Clerkship Committee, and has served as co-chairman of the Course Directors Committee and as a member of the Curriculum Committee. He also serves on the Advisory Committee for the UTMB and UTMB-UT Austin MD/PhD Combined Degree Programs. Dr. Rabek’s has ongoing educational research interests in the analysis of factors that affect the admission of underrepresented minority and economically disadvantaged applicants into medical school and the factors that affect the performance of academically at-risk students in the medical school curriculum. At the state level, Dr. Rabek serves on the Advisory Council for the Joint Admissions Medical Program (JAMP) and the Advisory Board for the Texas Medical and Dental School Admissions Service (TMDSAS).
Sandra Riegle, Ph.D.

Sandra Riegle, Ph.D, academic background includes a Ph.D. in Education/Curriculum and Instruction (Curriculum Studies and Social Studies) from Texas Tech University, and a Master’s degree in Political Science from Illinois State University. Presently, she is a post-doc at UTMB.

Daniel Traber, Ph.D.

Daniel Traber, Ph.D., is a Charles Robert Allen Professor of Anesthesiology at the University of Texas Medical Branch and a Professor of Neuroscience and Cell Biology. He serves as the Director of the Investigative Intensive Care Unit at UTMB and at the Shriners Hospital For Children. Following his studies at St. Mary's University, he acquired his Ph.D. in Physiology at UTMB. He studied with M. Mason Guest, the discoverer of urokinase and the dynamic changes in the red blood cell as it traversed the microvasculature, and his dissertation described erythrocyte fibrinogen interaction. After postdoctoral work in Pharmacology at Ohio State University with Robert Gardier, Dr. Traber was recruited back to Galveston to establish cardiopulmonary research laboratory at the Shriners Burns Institute. With exception of a one year sabbatical at the Boltzman Institute of Traumatology in Vienna, Austria with Professors Günther Schlag and Heinz Redl, Dr. Traber has been in Galveston since that time. He has published over 435 articles and 73 reviews and book chapters in the areas of shock, sepsis, and acute lung injury. He is the member of many National and International societies and was first to receive the Distinguished Teaching Award and Distinguished Alumni award of the UTMB Graduate School of Biomedical Sciences.
2009 50th National Student Research Forum

Schedule of Events

WEDNESDAY, April 22, 2009

4:00 pm – 7:00 pm  Registration Table Open
                  Lobby – Hilton Galveston Island Resort

6:00 pm – 8:00 pm  Kick-off Party with Refreshments and Appetizers
                  Poolside – Hilton Galveston Island Resort

8:00 pm – 10:00 pm Hospitality Suite Open – Hilton Galveston Island Resort

THURSDAY, April 23, 2009

7:30 am – 5:00 pm  Judge Lounge – Leeward Boardroom
                  NSRF Committee Office – Windward Boardroom

7:30 am – 4:00 pm  Registration Table Open
                  Foyer – Galveston Convention Center

7:30 am – 9:00 am  Continental Breakfast
                  Foyer – Galveston Convention Center

8:30 am – 9:00 am  Welcome Address
                  Galleon I & II – Galveston Convention Center

9:00 am – 10:15 am Oral Session A: Orthopedic Medicine and Surgery
                  Harbor Room – Galveston Convention Center
                  Oral Session B: Public Health and Medical Humanities
                  Spinnaker Room – Galveston Convention Center
                  Oral Session C: Biochemistry and Cell Biology
                  Schooner Room – Galveston Convention Center

10:15 am – 10:30 am Break

10:30 am – 12:00 pm Oral Session A – continued
                  Harbor Room – Galveston Convention Center
                  Oral Session B - continued
                  Spinnaker Room – Galveston Convention Center
                  Oral Session C - continued
                  Schooner Room – Galveston Convention Center

12:00 pm – 1:00 pm Lunch
                 Galleon I & II – Galveston Convention Center
1:00 pm – 1:50 pm  Focus group A: Infectious Disease and Biocontainment Thomas Ksiazek, D.V.M., Ph.D.; UTMB – Chief, Disease Assessment Section, Special Pathogens Branch, G14 Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control Atlanta, GA Harbor Room – Galveston Convention Center

Focus group B: Medicine and Space “Luna: What Did We Learn and What Should We Expect?” William Wallace, Ph.D.; NASA Spinnaker Room – Galveston Convention Center

Focus group C: Telemedicine and Global Health Alexander H. Vo, Ph.D.; UTMB – Executive Director AT&T Center for Telehealth Research and Policy Electronic Health Network Schooner Room – Galveston Convention Center

Focus group D: Prisoners as Research Subjects Jason Glenn, Ph.D.; UTMB - Assistant Professor Affiliations: Institute for the Medical Humanities Clipper Room – Galveston Convention Center

2:00 pm – 2:50 pm  Focus Groups Continued

4:00 pm – 5:00 pm  Abreu Keynote Memorial Lecture Series: “Social life of mitochondria within the cell: dynamic clubs, connected networks and depolarized singles” Orian Shirihai, M.D., Ph.D. Boston University School of Medicine Galleon I & II – Galveston Convention Center

7:00 pm – 10:00 pm  Hospitality Suite Open – Hilton Galveston Island Resort

FRIDAY, April 24, 2009

8:00 am – 5:00 pm  Judge Lounge – Leeward Boardroom NSRF Committee Office – Windward Boardroom

8:00 am – 4:00 pm  Registration Foyer – Galveston Convention Center

8:00 am – 9:00 am  Continental Breakfast Foyer – Galveston Convention Center

9:00 am – 10:15 am  Oral Session D: Microbiology and Immunology Harbor Room – Galveston Convention Center
Oral Session E: Neuroscience
Schooner Room – Galveston Convention Center

Oral Session F: Oncology and Cancer Cell Biology
Spinnaker Room – Galveston Convention Center

10:15 am – 10:30 am Break

10:30 am – 12:00 pm Oral Session D - continued
Harbor Room– Galveston Convention Center

Oral Session E - continued
Schooner Room – Galveston Convention Center

Oral Session F - continued
Spinnaker Room– Galveston Convention Center

12:00 pm – 1:30 pm Bench to Bedside Lunch
“The Ethics of Pharmaceutical Companies and Research”
Exhibit Hall A – Galveston Convention Center
Howard Brody, M.D., Ph.D. - Director, Institute for the Medical Humanities, Family Medicine John P. McGovern Centennial Chair
Alan Barrett, Ph.D. - UTMB Vaccines Expert
Martin G. Myers, M.D. - Adjunct Professor, Pediatrics, Preventive Medicine, Community Health

2:00 pm – 4:00 pm Poster Session 1
Foyer – Galveston Convention Center

4:00 pm – 5:00 pm Abreu Keynote Memorial Lecture Series:
“What if you could clone all the genes that cause cancer?
Making sense of the oncogenome.”
David Ferrick, Ph.D.
Chief Scientific Officer, Seahorse Bioscience
Exhibit Hall A – Galveston Convention Center

7:00 pm -9:00 pm Poolside Mixer
Refreshments, appetizers and entertainment
Poolside – Hilton Galveston Island Resort

9:00 pm – 11:00 pm Hospitality Suite Open – Hilton Galveston Island Resort

SATURDAY, April 25, 2009

8:30 am – 5:00 pm Judge Lounge – Hilton Galveston Island Resort
NSRF Committee Office – Hilton Galveston Island Resort

8:30 am – 10:00 am Continental Breakfast
Foyer – Hilton Galveston Island Resort
10:00 am – 12:00 pm
Poster Session 2
Hilton Galveston Island Resort

12:00 pm – 1:30 pm
Lunch
“The Power of Procrastination”
Jorge Cham, Ph.D.
Ph.D. Comics
Crystal Ballroom – Hilton Galveston Island Resort

1:30 pm – 3:00 pm
Translational Workshop
“Cellular Bioenergetics for the 21st Century”
David Ferrick, Ph.D.
Chief Scientific Officer, Seahorse Bioscience
Crystal Ballroom – Hilton Galveston Island Resort

3:00 pm – 6:00 pm
Hospitality Suite Open – Hilton Galveston Island Resort

6:00 pm – 8:00 pm
NSRF Awards Banquet
Grand Ballroom – Hilton Galveston Island Resort

9:00 pm – 1:00 am
NSRF After Party – Yaga’s Café Bar
2314 Strand

SUNDAY, April 26, 2009

8:00 am – 10:00 am
Breakfast Buffet – Hilton Galveston Island Resort
IN APPRECIATION

The 2009 National Student Research Forum Committee wishes to thank the following individuals and organizations for helping to make this year’s forum a success:

- AMA Foundation for their continued support of a great student run event.
- University of Texas Medical Branch administration for their never-ending help in all aspects of making the NSRF great.
- Faculty at the University of Texas Medical Branch and various off-campus institutions for their enthusiastic efforts in evaluating manuscripts, poster and oral presentations.
- Medical and graduate students at the University of Texas Medical Branch who served in many essential capacities.
- Dr. David L. Callender, President of the University of Texas Medical Branch, for his enthusiastic support and help with the NSRF.
- Dr. Garland Anderson, Provost and Dean of Medicine at the University of Texas Medical Branch, for his advocacy and support of the forum.
- Dr. Cary Cooper, Dean of the Graduate School of Biomedical Sciences at the University of Texas Medical Branch, for his continued advocacy and support of the forum.
- Dr. Lauree Thomas, Associate Dean for Student Affairs and Admissions at the University of Texas Medical Branch, for her enthusiastic encouragement.
- Dr. Jeffrey Rabek, Assistant Dean for Admissions at the University of Texas Medical Branch, for his years of dedication and support of the forum.
- Drs. Judith Aronson, Randall Given, Sandra Riegle and Daniel Traber, the 2009 National Student Research Forum Faculty Advisors, for their commitment, guidance, and dedication to the forum.
- Drs. Thomas Ksiazek William Wallace, Alexander Vo and Jason Glenn, for their aid in making the Bench to Bedside lunch possible.
- Drs. Howard Broodie, Alan Barrett and Marty Meyers, for their assistance in Coordinating the Focus Groups.
- Glenda McKinney, for her advocacy of the forum and proofreading help of many manuscripts.
- Drs. David Ferrick and Orian Shirihai for their time and efforts in speaking at the forum.
- The staff of the Office of Student Affairs and Admissions at the University of Texas Medical Branch for their assistance and dedication to the forum.
- Elisabeth Sanders for her dedication to making this year’s NSRF a success. Without her many hours of work, there would be no forum.
NATIONAL STUDENT RESEARCH FORUM JUDGES AND MANUSCRIPT REVIEWERS

The NSRF Co-Directors would like to thank the physicians and scientists who agreed to take time out of their busy schedules to review manuscripts and judge presentations. Their dedication to the future physicians and scientists is greatly appreciated.

NOTE: Some NSRF judging assignments had not been completed at the time of printing.

* Lutfi Abu-Elheiga, Ph.D.
Mahmoud Ahmed, Ph.D.
Ashraf Aly, M.D., Ph.D.
* Nicole Andrews, Ed.D.
Judith Aronson, M.D.
Emad Asham, M.D.
William Au, Ph.D.
Jose Barral, M.D., Ph.D.
John Bauer, M.D.
* Malavoelish Bikram, Ph.D.
* Joel Bloom, Ph.D.
Paul Boor, M.D.
Nigel Bourne, Ph.D.
* Audrius Brazdeikis, Ph.D.
Nataliya Bulayeva, Ph.D.
Gerald Campbell, M.D., Ph.D.
* Susan Carlton, Ph.D.
Dai Chung, M.D.
Robert Cox, Ph.D.
* Patricia Dahia, M.D., Ph.D.
* Farhad Danesh, M.D.
Larry Denner, Ph.D.
Anthony DiNuzzo, Ph.D.
* Mark Entman, M.D.
* Jason Erikson, Ph.D.
Li Fang, M.D., Ph.D.
* David Ferrick, Ph.D.
Celeste Finnerty, Ph.D.
* Charles Fulhorst, D.V.M., Ph.D.
* Gary Gallick, Ph.D.
Nisha Garg, Ph.D.
Randall Given, Ph.D.
Jason Glenn, Ph.D.
Emilio Gonzalez, M.D.
James Grady, Dr.P.H.
Owen Hamill, Ph.D.
* Shuhua Han, M.D.
Hal Hawkins, M.D.
Tapas Hazra, Ph.D.
Mark Hellmich, Ph.D.
Norbert Herzog, Ph.D.
Vincent Hilsen, Ph.D.
* Heidi Hofer, Ph.D.
Peter Hoffmann, M.D., M.Phil
Claire Hulsebosch, Ph.D.
* Kristina Hulten, Ph.D.
Sunil Jain, M.D.
Mohammad Jamaluddin, Ph.D.
* Ben Jansen, Ph.D.
Marc Jeschke, M.D., Ph.D.
* Daoyun Ji, Ph.D.
* Charles Kaplan, Ph.D.
Brent Kelly, M.D.
Lois Killewich, M.D., Ph.D.
* Joe Knezetic, Ph.D.
* Brian Knoll, Ph.D.
* Charles Kuszynski, Ph.D.
* John Ladbury, Ph.D.
James Lee, Ph.D.
* Mong-Hong Lee, Ph.D.
* Scott LeMaire, M.D.
* Eastwood Leung, Ph.D.
Simon Lewis, Ph.D.
Lillian Lockhart, M.D.
Michael Malloy, M.D.
A vi Markowitz, M.D.
* Bradley McConnell, Ph.D.
Evelyn McKinney, Ph.D.
Anita Mercado, M.D.
Radhesyam Miryala, M.D.
Sankar Mitra, Ph.D.
* Read Montague, Ph.D.
Tatiana Nanovskaya, D.D.S., Ph.D.
* Daniel O’Connor, Ph.D.
Stobdan Prasler, D.V.M., Ph.D.
Vinod Panchbhavi, M.D.
Janak Patel, M.D.
Konrad Pazdruk, Ph.D.
Silvia Perelangeli, Ph.D.
* Thomas Pressley, Ph.D.
* Rick Puzdrowski, Ph.D.
Jeffrey Rabek, Ph.D.
Krishna Rajarathnam, Ph.D.
Adrian Recinos, Ph.D.
Sandra Riegle, Ph.D.
Nancy Robinson, M.D.
* John Rodgers, M.D., M.P.H.
Jose Rojas, Ph.D., R.R.T.
National Student Research Forum Awards

The purpose of the awards program is to encourage and recognize outstanding research in basic and clinical sciences. Availability of an award does not necessarily guarantee its presentation. Research papers must be judged to be of sufficient quality to merit receipt of an award.

Overall Awards
AMAF Award for Excellence in Clinical Research
AMAF Award for Excellence in Basic Research

Awards for Best Oral Presentations
UTMB School of Medicine, Office of Student Affairs Outstanding Oral Presentation First Place
NSRF Outstanding Oral Presentation Second Place
NSRF Outstanding Oral Presentation Third Place

Awards for Best Poster Presentations
UTMB School of Medicine, Office of Student Affairs Outstanding Poster Presentation First Place
NSRF Outstanding Poster Presentation Second Place
NSRF Outstanding Poster Presentation Third Place

Categorical Awards
Best Oral Presentation in Surgery and Orthopedic Medicine
Best Oral Presentation in Medical Humanities and Public Health
Best Oral Presentation in Biochemistry and Cell Biology
Best Oral Presentation in Microbiology and Immunology
Best Oral Presentation in Neuroscience
Best Oral Presentation in Oncology and Cancer Cell Biology
Best Poster Presentation in Cardiology
Best Poster Presentation in Dermatology
Best Poster Presentation in Obstetrics and Gynecology
Best Poster Presentation in Orthopedic Medicine
Best Poster Presentation in Physiology
Best Poster Presentation in Public Health
Best Poster Presentation in Radiology
Best Poster Presentation in Surgery
Best Poster Presentation in Biochemistry
Best Poster Presentation in Cell Biology
Best Poster Presentation in Genetics
Best Poster Presentation in Immunology
Best Poster Presentation in Microbiology and Infectious Disease
Best Poster Presentation in Neuroscience
Best Poster Presentation in Oncology
Best Poster Presentation in Pathology
Best Poster Presentation in Pharmacology and Toxicology
The Oslerian Award for Translational Research
Sponsored by Judith F. Aronson, MD, William Osler Scholar, John P. McGovern Academy of Oslerian Medicine

“The…greatest glory is that the leaves of the tree of science have availed for the healing of the nations. Measure as we may the progress of the world – intellectually in the growth and spread of education, materially in the application to life of all mechanical appliances, and morally in a higher standard of ethics between nation and nation, and between individuals, there is no one measure which can compare with the decrease of disease and suffering in man, woman and child.”
-Sir William Osler

*Man’s Redemption of Man: A Lay Sermon, 1910*

The John P. McGovern Academy of Oslerian Medicine was created in 2001 as a result of the combined visions of Dr. John McGovern and Dr. John Stobo. The Academy was founded to foster the ideals for which Sir William Osler is most revered: scientifically based medical practice, personalized care of patients with emphasis on the doctor-patient relationship, and a commitment to professionalism. As part of its mission, the Academy supports faculty and student Osler scholars. Dr. Aronson, a pathologist, was elected to the Academy in 2004. She sponsors the Oslerian Award for Translational Research to recognize those NSRF participants who best articulate the relevance of their research to Oslerian principles of science, compassion, and humanism.

To compete for this award, the applicant will write an original 1000-word essay describing the implications and potential importance of his/her research avenue or discovery for the betterment of human health. The successful essay should explicitly link results of the applicant’s scientific inquiry with humanistic ideals espoused by Osler and emulated to this day. Judging will be based both on the applicant’s essay and submitted abstract. Up to five winners will receive this award.
DETERMINATION OF AWARDS

The National Student Research Forum offers several categorical and overall awards.

Each poster presentation is evaluated by the average score from three different on-site judges. Each oral presentation is evaluated by a combined score from three on-site judges and three off-site manuscript judges. The manuscript average score accounts for 60% of the overall score, with the average of the presentation scores making up the remaining 40%. Presenters are then ranked based on their scores and the top ones are qualified for awards in their field of competition. All comments of evaluators are taken into consideration when determining ties among presenters.

Participants are eligible to compete for only one Categorical Award in their respective field of research and for only one AMAF or Overall Award.

Any faculty member participating in the National Student Research Forum as an oral/poster presentation judge cannot be listed as an author on any paper competing for an award in the session for which they are a judge.

American Medical Association Foundation Overall Awards

These awards are given to the two presenters who exemplify excellent skills in Basic or Clinical Research and have accumulated outstanding total scores in their presentations.

Best Oral/Poster Awards

These awards are given to three oral and three poster presenters who exhibit the highest scores in their respective presentation.

Categorical Awards

These awards are given to presenters who exhibit the highest scores within their respective categories of research.
“Social life of mitochondria within the cell: dynamic clubs, connected networks and depolarized singles”

Orian Shirihai, M.D., Ph.D.

Founder of the Mitochondria Advancing Research through Collaborations
Director of the Cellular Imaging Core at Boston University School of Medicine
University of Boston Medical Center, Department of Medicine

Orian Shirihai, M.D., Ph.D. joined the Tufts School of Medicine's Department of Pharmacology and Experimental Therapeutics in December 2003. Before Tufts, Dr. Shirihai trained in the Marine Biological Laboratory in Woods Hole, Massachusetts, where he founded the Laboratory for Molecular Physiology of Mitochondria in 2001. Prior to Woods Hole, Shirihai did postdoctoral work in Stuart H. Orkin, M.D.'s laboratory at Harvard. He earned his MD and PhD degrees from the faculty of medicine at the Technion—Israel Institute of Technology, where his research uncovered the roles of membrane potential in blood cell differentiation.
“What if you could clone all the genes that cause cancer? Making sense of the Oncogenome”

David Ferrick, Ph.D.
Chief Scientific Officer, Seahorse Bioscience Inc.
Founder and CEO, Sagres Discovery
Founder, Boehringer Ingelheim Corporation
University of California, Davis Department of Pathology, Microbiology & Immunology

Dr. Ferrick has over 20 years of R&D experience in drug discovery, clinical development and life science applications. As an industry executive he has transformed three biotechnology research platforms into product pipelines, founded one of those companies, raised over $30M in private equity and established several corporate alliances including Pfizer, Novartis and Boehringer Ingelheim.

He currently is the Chief Scientific Officer at Seahorse Biosciences, a privately held Boston area biotechnology company that designs and manufactures instruments and consumable sensors that measure in real time the uptake and excretion of metabolic end products. Prior to joining Seahorse Bioscience, Dr. Ferrick directed Biology and Application Development at Guava Technologies, a cell-based instrument and applications company. In 1999, Dr. Ferrick founded and led Sagres Discovery, an oncogenome research and cancer drug discovery company until it was acquired by Chiron in 2004. Prior to that Dr. Ferrick was the head of Molecular and Cellular Biology at Rigel Pharmaceuticals Inc. since its inception in 1997. Dr. Ferrick received his Ph.D. in Microbiology from Georgetown University and did his postdoctoral fellowship with Dr. Tak Mak. Dr. Ferrick held a faculty position at the University of California at Davis, where his contributions to the discovery and functions of gamma T cells have made him a world-recognized leader in this area. He has authored over 90 peer-reviewed publications, 25 patents and has been awarded over $3M in NIH research funding.
Oral Presentations

All participants in the oral presentation category that submitted a manuscript for review will be considered for Overall Awards and Oral Categorical Awards. Information regarding how the awards are selected can be found on page 27 of this program.
<table>
<thead>
<tr>
<th>Session</th>
<th>Speaker</th>
<th>Affiliation</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-1</td>
<td>Friel, Nicole</td>
<td>Rush University Medical Center</td>
<td>THE EFFECT OF HIGHLY PURIFIED CAPSAICIN ON NORMAL ARTICULAR CARTILAGE AND ROTATOR CUFF TENDON HEALING: AN IN VIVO RABBIT STUDY</td>
</tr>
<tr>
<td>A-2</td>
<td>Ding, Anthony</td>
<td>Columbia University College of Physicians and Surgeons</td>
<td>ATYPICAL FEMORAL FRACTURES ASSOCIATED WITH LONG-TERM BISPHOSPHONATE TREATMENT</td>
</tr>
<tr>
<td>A-3</td>
<td>Cox, Joseph</td>
<td>UAB School of Medicine</td>
<td>THE USE OF A BIODEGRADABLE, LOAD-BEARING SCAFFOLD AS A CARRIER FOR ANTIBIOTICS IN AN INFECTED OPEN FRACTURE MODEL</td>
</tr>
<tr>
<td>A-4</td>
<td>Cassilly, Ryan</td>
<td>Columbia University College of Physicians and Surgeons</td>
<td>TENSILE PROPERTIES OF THE SIMIAN INFERIOR GLENOHUMERAL LIGAMENT</td>
</tr>
<tr>
<td>A-5</td>
<td>Spotnitz, Matthew</td>
<td>Columbia University College of Physicians and Surgeons</td>
<td>INTRAOPERATIVE HEMODYNAMIC STABILITY OF PATIENTS DURING BIVENTRICULAR PACING AFTER CARDIAC SURGERY: RESULTS FROM THE BIPACS TRIAL</td>
</tr>
<tr>
<td>A-6</td>
<td>Bykowski, Michael</td>
<td>University of Pittsburgh</td>
<td>INKJET-BASED BIO-PRINTING OF BONE MORPHOGENETIC PROTEIN AND NOGGIN TO SPATIALLY CONTROL BONE FORMATION IN VIVO</td>
</tr>
</tbody>
</table>
50th Annual NSRF
Public Health and Medical Humanities
Oral Session B
Thursday, April 23, 2009
9:00 am
Spinnaker Room

B-1  Bindawas, Saad  
University of Texas Medical Branch  
9:15  IMPACT OF LOWER EXTREMITY PERFORMANCE ON HEALTH-RELATED QUALITY OF LIFE IN OLDER MEXICAN AMERICANS

B-2  Raza, Sajjad  
Dow University of Health Sciences, Karachi, Pakistan.  
9:30  PREVALENCE AND EFFECT ON DISEASE SEVERITY OF HEPATITIS D IN HEPATITIS B SURFACE ANTIGEN POSITIVE PATIENTS

B-3  Nam, Sang Gon  
University of Texas Medical Branch  
9:45  THE EFFECT OF MEDICAL CONDITIONS ON ACTIVITY LIMITATIONS IN OLDER MEXICAN-AMERICANS

B-4  Lee, Eun-Ju  
Columbia University College of Physicians and Surgeons  
10:00  EFFECT OF LAPAROSCOPIC ADJUSTABLE GASTRIC BANDING (LAGB) ON METABOLIC SYNDROME & ITS RISK FACTORS IN MORBIDLY OBESE ADOLESCENTS

B-5  Lee, Leslie  
Columbia University College of Physicians and Surgeons  
10:30  TEMPORAL TRENDS IN STROKE CARE IN THE UNITED STATES, 1998 - 2006

B-6  Kasten, Jennifer  
Columbia University College of Physicians and Surgeons  
10:45  ON SPONGE-GRAFTING: REDISCOVERY OF A HISTORICAL PLASTIC SURGERY TECHNIQUE

B-7  White, Christopher  
University of Manitoba  
11:00  A COMMON REFERRAL SYSTEM FOR GENERAL SURGERY – IMPACT ON WAITING TIMES AND ACCEPTABILITY AMONG REFERRING PHYSICIANS

B-8  Jordan, Lindsey  
University of Texas Medical Branch  
11:15  INFANT OBESITY IN PEDIATRIC PRACTICE

B-9  Abejuela, Harmony  
David Geffen School of Medicine at the University of California  
11:30  HEALTH SEEKING BEHAVIORS, HEALTH SERVICES UTILIZATION, AND RECEIPT OF COUNSELING BY CLINICIANS AMONG LATINO PATIENTS IN PUBLIC SECTOR CLINICS

B-10  Kent, David  
Columbia University College of Physicians and Surgeons  
11:45
LINKAGE AND ASSOCIATION MODELING OF CANDIDATE GENES IN NON-
SYNDROMIC CLEFT LIP AND PALATE IN THE HONDURAN POPULATION

50th Annual NSRF
Biochemistry and Cell Biology
Oral Session C
Thursday, April 23, 2009
10:30 am
Schooner Room

C-1  Davis, Carter
9:15   Louisiana State University Health Sciences Center - School of Medicine
ROCK ACTIVITY REGULATES TUMOR CELL ADHESION

C-2  Chen, Daisi
9:30   University of Texas Medical Branch
THE ROLE OF MOLECULAR CHAPERONE UNC-45A IN HUMAN BREAST CANCER

C-3  Rubinstein, Tal
9:45   Saint Louis University School of Medicine
THE ROLE OF ß-ARRESTIN2 IN MORPHINE INHIBITION OF EGF-INDUCED
PROLIFERATION OF ASTROCYTES

C-4  Sakabe, Kaoru
10:00  Johns Hopkins University
COACTIVATOR ASSOCIATED ARGinine METHYLTRANSFERASE CONFERS
SUBSTRATE SPECIFICITY FOR O-GLCNAC TRANSFERASE

C-5  Agarwal, Udit
10:30  Kent State University
CXCR4 REGULATION IN CARDIAC MYOCYTES AFTER HYPOXIC INJURY

C-6  Ewing, Jason
10:45  LSU School of Medicine New Orleans
A NOVEL ROLE OF Gaz and Gaq SUBUNIT PROTEINS IN CENTRAL a1 AND a2
ADRENERGIC RECEPTOR-MEDIATED CHANGES IN CARDIOVASCULAR AND
RENAL FUNCTION IN CONSCIOUS SPRAGUE-DAWLEY RATS
50th Annual NSRF
Microbiology and Immunology
Oral Session D
Friday, April 24, 2009
9:00 am
Harbor Room

D-1  Davis, Katie
9:15  University of Alabama at Birmingham
HIV-2/HIV-1 ENVELOPE CHIMERAS DETECT HIGH TITER BROADLY REACTIVE HIV-1 V3-SPECIFIC ANTIBODIES IN HUMAN PLASMA

D-2  Baggerman, Eric
9:30  University of Texas Medical Branch
ROLE OF AMNIOTIC FLUID IN REDUCING AND/OR PREVENTING NECROTIZING ENTEROCOLITIS IN EXPERIMENTAL PREMATURE NEONATAL RAT MODEL

D-3  Huang, Alexander
9:45  Mount Sinai School of Medicine
TOLL-LIKE RECEPTOR AGONISTS SYNERGIZE WITH CD40L/IFN. TO PROMOTE HUMAN DENDRITIC CELL SYNTHESIS OF IL-12

D-4  Dao, Doan
10:00 The University of Texas Southwestern Medical Center at Dallas
HOST RESPONSES AND VIROLOGIC PROFILES IN PATIENTS WITH ACUTE LIVER FAILURE SECONDARY TO ACUTE HEPATITIS B VIRUS (HBV) INFECTION OR ACUTE EXACERBATION OF CHRONIC HBV

D-5  Xue, Qiong
10:30 Institute of Biosciences and Technology, Texas A&M University
INTERNALIZATION MECHANISMS OF BACILLUS ANTHRACIS SPORES BY HOST EPITHELIAL CELLS

D-6  Chapman, Timothy
10:45 University of Rochester, Rochester, NY
VLA-1 DEPENDENT ACCUMULATION OF A POPULATION OF EFFECTOR MEMORY CD4+ T CELLS TO THE LUNG FOLLOWING INFLUENZA INFECTION

D-7  Hillman, China-Li
11:00 University of Manitoba
TARGETING IL-12/23P40 USING VACCINES AMELIORATES MURINE CHRONIC CO-LITIS
<table>
<thead>
<tr>
<th>Session</th>
<th>Speaker 1</th>
<th>Institution 1</th>
<th>Title 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-1</td>
<td>Deshpande, Abhishek</td>
<td>Cleveland Clinic / Kent State University</td>
<td>CHRONIC HYDROCEPHALUS INDUCED ISCHEMIC CHANGES RELATING TO BLOOD VESSEL DENSITY AND VEGFR-2 IN CAUDATE NUCLEUS AFTER SHUNTING</td>
</tr>
<tr>
<td>E-2</td>
<td>Davis, Shanlee</td>
<td>Mayo Clinic College of Medicine</td>
<td>EPILEPSY IN CHILDREN WITH ADHD</td>
</tr>
<tr>
<td>E-3</td>
<td>Shwe, Yamin</td>
<td>Boston University School of Medicine</td>
<td>MATURATION OF ADULT GENERATED NEURONS IN THE DENTATE GYRUS OF AGING RHESUS MONKEYS</td>
</tr>
<tr>
<td>E-4</td>
<td>Sharp, Michelle</td>
<td>LSU School of Medicine New Orleans</td>
<td>NEUROPROTECTIN D1 MEDIATES CELL SURVIVAL IN AN IN VITRO MODEL OF PARKINSON’S DISEASE</td>
</tr>
<tr>
<td>E-5</td>
<td>Lasagna Reeves, Cristian</td>
<td>University of Texas Medical Branch</td>
<td>TARGETING AMYLOID OLIGOMERS FOR DIAGNOSIS AND TREATMENT FOR ALZHEIMER’S DISEASE</td>
</tr>
<tr>
<td>E-6</td>
<td>Leitzke, Arthur</td>
<td>Loma Linda University</td>
<td>MATERNAL LOW PROTEIN DIET: DEVELOPMENTAL ORIGIN OF ADULT HYPERTENSION</td>
</tr>
<tr>
<td>Session</td>
<td>Title</td>
<td>Speaker</td>
<td>Affiliation</td>
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</tr>
<tr>
<td>F-1</td>
<td>ANALYSIS OF SURVIVAL TRENDS IN PATIENTS WITH METASTATIC BREAST CANCER RECEIVING CHEMOTHERAPY: AN INSTITUTIONAL OVERVIEW</td>
<td>Gupta, Ravi</td>
<td>Case Western Reserve University School of Medicine</td>
</tr>
<tr>
<td>F-2</td>
<td>EFFECT OF TARGETED INHIBITION OF mTOR COMPLEXES ON PROLIFERATION, APOPTOSIS AND CELL CYCLE PROGRESSION IN COLORECTAL CANCER</td>
<td>Gulhati, Pat</td>
<td>University of Texas Medical Branch</td>
</tr>
<tr>
<td>F-3</td>
<td>THE UTILITY OF TISSUE DOPPLER IMAGING, CARDIAC BIOMARKERS, AND CARDIAC MRI IN PREDICTING EARLY LEFT VENTRICULAR DYSFUNCTION IN PATIENTS WITH HER-2 POSITIVE BREAST CANCER TREATED WITH HERCEPTIN</td>
<td>Fallah-Rad, Nazanin</td>
<td>University Of Manitoba, Faculty of Medicine</td>
</tr>
<tr>
<td>F-4</td>
<td>APPLYING PROTEOMICS BASED MASS SPECTROMETRY IMAGE PROFILING TOOLS TO PANCREATIC CANCER</td>
<td>Shubert, Christopher</td>
<td>University Of Alabama School of Medicine</td>
</tr>
<tr>
<td>F-5</td>
<td>PREOPERATIVE C-REACTIVE PROTEIN LEVELS PREDICT METASTASIS AND 1-YEAR MORTALITY IN PATIENTS RECEIVING POTENTIALLY CURATIVE NEPHRECTOMY FOR LOCALIZED RENAL CELL CARCINOMA</td>
<td>Johnson, Timothy</td>
<td>Emory University School of Medicine</td>
</tr>
<tr>
<td>F-6</td>
<td>UTILITY OF TISSUE DOPPLER AND STRAIN IMAGING IN THE EARLY DETECTION OF TRASTUZUMAB AND ANTHRACYCLINE MEDIATED CARDIOMYOPATHY</td>
<td>Han, Cecelia (Song-Yee)</td>
<td>University of Manitoba</td>
</tr>
<tr>
<td>F-7</td>
<td>CHARACTERIZATION AND TARGETING OF THERAPY-RESISTANT MANTLE CELL LYMPHOMA</td>
<td>Nordgren, Tara</td>
<td>University of Nebraska Medical Center</td>
</tr>
</tbody>
</table>
Poster Presentations

All poster presentations are eligible for the Poster Presentation Overall Awards and Categorical Awards that apply. Information regarding how the awards are selected can be found on page 27 of this program.
50th Annual NSRF
Cardiology
Poster Session 1
Friday, April 24, 2009
2:00 pm
Galveston Convention Center Foyer

1 Gonzalez, Maday
   Albert Einstein College of Medicine
   INDUCED BRUGADA TYPE ECG, A SIGN FOR IMMINENT MALIGNANT ARRRHYTHMIAS

2 Wang, Jun
   Institute of Biosciences and Technology, Texas A&M System
   PITX2: LINKING ATRIAL FIBRILLATION AND LEFT-RIGHT ASYMMETRY

3 Caldwell, Kenneth
   University of Texas Medical Branch
   AORTIC SINUS WALL DIMENSIONS AND GEOMETRY IN FRESH AUTOPSY SPECIMENS

4 Rajendra, Rashmi
   University of South Alabama College of Medicine
   THE NORMAL AND ABNORMAL OWL MONKEY (AOTUS SP.) HEART: LOOKING AT CARDIOMYOPATHY CHANGES WITH ECHOCARDIOGRAPHY AND ELECTROCARDIOGRAPHY

5 Lee, Leslie
   Columbia University College of Physicians and Surgeons
   HYPOTHERMIA AFTER ACUTE ISCHEMIC STROKE: IS LESS MORE?

6 Weekley Minnich, Lauren
   University of Texas Health Science Center at San Antonio
   ASCENDING AORTIC ANEURYSM IN A HIV+ PATIENT

7 Gladden, James
   University of Alabama at Birmingham
   INHIBITION OF XANTHINE OXIDASE IMPROVES LEFT VENTRICULAR DIASTOLIC FUNCTION AND MITOCHONDRIAL FUNCTION IN ACUTE VOLUME OVERLOAD IN THE RAT HEART
8  D'Souza, Logan  
*University of Oklahoma College of Medicine (Tulsa)*  
ATYPICAL MYCOSIS FUNGOIDES PRESENTATION IN CHILD

9  Scroggins, Leslie  
*University of Texas Medical Branch*  
MATRIX METALLOPROTEINASE EXPRESSION IN NEPHROGENIC SYSTEMIC FIBROSIS

10  Pugashetti, Rupa  
*University of California, Irvine School of Medicine*  
DERMAL MUCINOSIS AS A SIGN OF VENOUS INSUFFICIENCY

11  Shiue, Lisa  
*University of Texas Health Science Center at Houston-Graduate*  
INCREASED LEVELS OF CD4+25high REGULATORY T CELLS IN PATIENTS WITH CUTANEOUS T-CELL LYMPHOMA AFTER EXTRACORPOREAL PHOTOPHERESIS

12  Landry, Adaira  
*David Geffen at University of CA, Los Angeles*  
TAZAROTENE'S CHEMOPREVENTION EFFICACY ON PRECLINICAL MODELS OF MEDULLOBLASTOMA AND BASAL CELL CARCINOMA

13  Clos, Audra  
*University of Texas Medical Branch*  
PASSIVE IMMUNOTHERAPY FOR THE TREATMENT OF CUTANEOUS AMYLOIDOSIS
14  **Bollineni, Vikram Rao**  
*Kharkiv National Medical University*  
**COMPARISION OF MECHANICAL VENTILATION REGIMEN IN PRE-TERM INFANTS WITH RESPIRATORY DISORDERS**

15  **Williams, Marian**  
*University of Texas Medical Branch*  
**OUTCOME OF CYTOLOGY AND PATHOLOGY REVIEW OF DISCORDANT CERVICAL CANCER SCREENING EVALUATIONS**
<table>
<thead>
<tr>
<th></th>
<th>Name</th>
<th>Institution</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>Zielsdorf, Shannon</td>
<td>Rush University Medical College</td>
<td>TWO-YEAR POST-OPERATIVE OUTCOMES OF ARTHROSCOPIC DOUBLE-ROW ROTATOR CUFF REPAIR</td>
</tr>
<tr>
<td>17</td>
<td>Dyrszka, Marc</td>
<td>Columbia University College of Physicians and Surgeons</td>
<td>PREDICTING OUTCOMES IN TOTAL SHOULDER ARTHROPLASTY USING 3-DIMENSIONAL COMPUTER SIMULATIONS</td>
</tr>
<tr>
<td>18</td>
<td>Arshin, Arshin</td>
<td>Louisiana State University Health Sciences Center</td>
<td>RADIATION-INDUCED INFERTILITY: A CONCERN IN HETEROPTIC OSSIFICATION PROPHYLAXIS?</td>
</tr>
<tr>
<td>19</td>
<td>Weber, Daniel</td>
<td>Loyola University Chicago Stritch School of Medicine</td>
<td>COMPARISON OF TOPICAL ANESTHESIA VERSUS PLACEBO PRIOR TO KNEE INJECTIONS</td>
</tr>
<tr>
<td>20</td>
<td>Bermudez, Luis</td>
<td>Texas Tech University Health Science Center in Lubbock</td>
<td>MORPHOMETRY BASED PERIPHERAL NERVE SURGERY DEVELOPMENT</td>
</tr>
<tr>
<td>21</td>
<td>Cassilly, Ryan</td>
<td>Columbia University - College of Physicians and Surgeons</td>
<td>MRI EVALUATION OF TERES MINOR HYPERTROPHY AND FUNCTIONAL STATUS IN PATIENTS WITH MASSIVE ROTATOR CUFF TEARS</td>
</tr>
<tr>
<td>22</td>
<td>Stephens, Byron</td>
<td>University of Tennessee Health Science Center College of Medicine</td>
<td>TYPE II ODONTOID FRACTURES IN THE ELDERLY: SURGERY VS. CONSERVATIVE MANAGEMENT</td>
</tr>
</tbody>
</table>
23 Boretsky, Adam  
University of Texas Medical Branch  
AUTOFLUORESCENCE IMAGING OF THE RETINAL PIGMENT EPITHELIUM TO MONITOR BENEFITS OF INDUCED HSP UPREGULATION IN RESPONSE TO PHOTOTHERMAL DAMAGE

24 Keenan, Peter  
Boston University School of Medicine  
AN EVALUATION OF LUNG MECHANICS DURING COMPUTER ASSISTED WEANING

25 Hashem, Jood  
Texas Tech University Health Sciences Center  
Na+/Ca2+ EXCHANGER OPERATES IN THE REVERSE MODE IN CORONARY MICROVASCULAR ENDOTHELIAL CELLS FROM NORMAL BUT NOT FROM DIABETIC RATS

26 Downey, Ryan  
Texas Tech University Health Sciences Center, Graduate  
NA,K PUMP ALPHA 4 SUBUNIT EXPRESSION IN HUMAN PROSTATE CELL LINES

27 Brinley, Alaina  
University of Texas Medical Branch  
Efficacy of Compression Garments to Simulate Fluid Shifts During Lunar Bedrest
28 Garde, Joanne  
*Pennsylvania State University College of Medicine*  
SURVEY OF DEMOGRAPHICS AND DIAGNOSES OF PATIENTS TO ASSESS PREVALENCE OF KNOWN HIV STATUS, ARV USE AND COMPLICATIONS, AND CLINICAL AIDS DIAGNOSIS IN PARIRENYATWA CENTRAL HOSPITAL IN HARARE, ZIMBABWE

29 Sakai, Lauren  
*Loyola University Chicago, Stritch School of Medicine*  
ALCOHOL USE DISORDER SCREENING IN EMERGENCY GENERAL SURGICAL PATIENTS: A COMPARISON OF TWO SITES

30 Kadikoy, Huseyin  
*Baylor College of Medicine*  
EXAMINATION OF PATIENTS’ WEIGHT REDUCTION EXPECTATIONS AND DESIRE FOR CO-MORBIDITY RISK REDUCTION PRIOR TO BARIATRIC SURGERY

31 Jeong, Su Jin  
*University of Alabama at Birmingham*  
DETERMINANTS OF ADEQUATE FOLLOW-UP OF AN ABNOMAL PAPANICOLAOU RESULT AMONG JAMAICAN WOMEN IN PORTLAND, JAMAICA

32 Abbasi, Ammara  
*Emory University School of Medicine*  
NUMERICAL LITERACY AND THE ABILITY TO ADVISE PATIENTS OF RISK: MULTI-INSTITUTIONAL STUDY OF MEDICAL STUDENTS AND UNDERGRADUATES

33 Messenger, Christopher  
*University of Texas Medical Branch*  
RACE DIFFERENCES IN SELF-ASSESSED HEALTH: THE ROLE OF JOB STRAIN

40 Mahaney, Patrick  
*SUNY at Buffalo*  
AGREEMENT OF ASSESSMENT METRICS IN THE DIAGNOSIS OF OBESITY
34 **Layer, Lauren**  
*University of Texas Medical Branch*  
INTRACRANIAL CATHETERIZATION USING A SACRAL HIATUS ACCESS AS AN ALTERNATIVE FOR PERCUTANEOUS INTRASPINAL NAVIGATION: A STUDY IN CADAVERS

35 **Jeffery, Dean**  
*University of Alberta*  
VESSEL MOVEMENT AND IMAGE QUALITY IN THE DIAGNOSIS OF ARTERIAL DISEASE WITH MRI

36 **Nukolova, Nataliya**  
*University of Nebraska Medical Center*  
DESIGN OF FOLIC ACID-CONJUGATED CROSS-LINKED POLYMER MICELLES FOR DELIVERY OF MAGNETIC RESONANCE IMAGING AGENTS
37  **Ward, Marc**  
*University of Chicago Pritzker School of Medicine*  
DUODENAL SWITCH PROVIDES SUPERIOR RESOLUTION OF METABOLIC COMORBIDITIES INDEPENDENT OF WEIGHT LOSS IN THE SUPER-OBESE (BMI = 50 kg/m²) COMPARED WITH GASTRIC BYPASS

38  **Khaja, Hena**  
*Mayo Clinic*  
TRABECTOME ABLATION ARC CLINICAL RESULTS AND RELATION TO INTRAOCULAR PRESSURE

39  **Karas, Vasili**  
*Rush University Medical College*  
OUTCOMES OF SUPERIOR LABRAL, ANTERIOR TO POSTERIOR (SLAP) TYPE II REPAIRS
50th Annual NSRF
Biochemistry
Poster Session 2
Saturday, April 25, 2009
10:00 am
Hilton Foyer

50  **Truong, Michael**  
*Medical College of Wisconsin*  
RAC1/RAC3 INTERACTION WITH SMGGDS-607 AND SMGGDS-558

51  **Al-Lahham, Rabab**  
*University of Texas Medical Branch*  
MITOCHONDRIAL-GENERATED ROS, THROUGH ACTIVATION OF THE STRESS RESPONSE PATHWAY, DOWNREGULATES THE INSULIN SIGNALING PATHWAY

52  **Saenz, David**  
*University of Texas Medical Branch*  
8-OXOGUANINE AS THE POSSIBLE CAUSE OF CELLULAR SENESCENCE

53  **Winters, David**  
*University of Texas Medical Branch*  
HNRNP-U’s INTERACTION WITH NEIL1 AND ITS ROLE IN NEIL1 INITIATED BASE EXCISION REPAIR
50th Annual NSRF
Cell Biology
Poster Session 2
Saturday, April 25, 2009
10:00 am
Hilton Foyer

54  Haeri, Mohammad
    SUNY Upstate Medical University
    BIREFRINGENCE BANDS IN ROD PHOTORECEPTORS ORIGINATE FROM
    DIURNAL VARIATION IN RHODOPSIN PACKING INTO OUTER SEGMENT DISC
    MEMBRANES

55  Guy, William
    Baylor College of Medicine
    DEPROTONATION OF DOCOSAHEXAENOIC ACID IS RESPONSIBLE FOR A
    HYPERPOLARIZING SHIFT OF PRESTIN-ASSOCIATED CHARGE MOVEMENT

56  Martin, Stephanie
    University of Texas Medical School at Houston
    MECHANISM OF GLUTAMINE’S EFFECT ON PEROXISOME PROLIFERATOR-
    ACTIVATED RECEPTOR-GAMMA

57  Kim, Junghyun
    University of Alabama at Birmingham
    CHROMATIN LOOPING BETWEEN AN INTRONIC ENHANCER AND DISTAL
    PROMOTER REGIONS REGULATES HUMAN HEME OXYGENASE-1 GENE

58  Kasten, Jennifer
    Columbia University College of Physicians and Surgeons
    TGF-β1 INHIBITS LYMPHATIC REGENERATION BY DIRECTLY INHIBITING
    LYMPHATIC ENDOTHELIAL CELL PROLIFERATION, DIFFERENTIATION AND
    INTEGRIN EXPRESSION, LEADING TO CLINICAL LYMPHEDEMA IN A MURINE
    SURGICAL MODEL

59  Johnson, Guyla
    University of Alabama at Birmingham
    A ROBUST, RELIABLE, AND FAST ASSAY TO IDENTIFY SMALL MOLECULES
    ENHANCING NUCLEAR FACTOR KAPPA B EXPRESSION IN HUMAN
    NEUROBLASTOMA CELLS

60  Potter, Adam
    Baylor College of Medicine
    GENE TARGETS OF IGF-IR SIGNALING AND THEIR ROLE IN BREAST CANCER

61  Bolisetty, Subhashini
    University of Alabama at Birmingham
    ROLE OF HEME OXYGENASE-1 IN CISPLATIN-MEDIATED AUTOPHAGY IN
    KIDNEY EPITHELIAL CELLS
62 Sohrab, Mahsa  
*Columbia University College of Physicians and Surgeons*  
ASSOCIATION OF HOMOZYGOUS HIGH-RISK ALLELES IN COMPLEMENT FACTOR H AND ARMS2 WITH DRUSEN STAGING OF AGE-RELATED MACULAR DEGENERATION (AMD)

63 Ziats, Mark  
*Baylor College of Medicine*  
KIDNEY AND MUSCLE PHENOTYPES DUE TO HYPOSIALYLATION IN A MOUSE MODEL OF HEREDITARY INCLUSION BODY MYOPATHY

64 Zhu, Zengrong  
*University of Texas Medical Branch*  
REGULATION OF NEURONAL MIGRATION IN THE DROSOPHILA VENTRAL NERVE CORD

65 Dhruve, Miten  
*University of Manitoba*  
DLX TRANSCRIPTIONAL REGULATION OF INSULIN EXPRESSION DURING PANCREATIC DEVELOPMENT

66 Chakravarthy, Harini  
*University of Nebraska Medical Center*  
TRANSCRIPTIONAL REGULATION OF SOX21, A POISED GENE IN EMBRYONIC STEM (ES) CELLS

67 Burke, Kelly  
*Columbia University College of Physicians and Surgeons*  
IDENTIFICATION OF GENE MUTATIONS WITHIN FAMILIES WITH MONOGENIC DISEASE THROUGH LINKAGE ANALYSIS

108 Rondelli, Catherine  
*University of Texas Medical Branch*  
HAPLOTYPE ANALYSIS OF THE FULL XPC GENOMIC SEQUENCE REVEALS A CLUSTER OF VARIANTS ASSOCIATED WITH SENSITIVITY TO THE GENOTOXIC EFFECTS OF TOBACCO SMOKE
<table>
<thead>
<tr>
<th>Post Number</th>
<th>Author</th>
<th>Affiliation</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>68</td>
<td>Starr, Marlene</td>
<td>University of Texas Medical Branch</td>
<td>Adipose tissue is a major source of IL-6 production and contributes to age-associated mortality during sepsis</td>
</tr>
<tr>
<td>69</td>
<td>Williams, Jessica</td>
<td>University of Texas Medical Branch</td>
<td>Dendritic cell modulation enhances neutrophil-mediated resistance to burn wound infection</td>
</tr>
<tr>
<td>70</td>
<td>Lancaster, Katrina</td>
<td>University of Texas Medical Branch</td>
<td>HIV-1 compromises CD8+ T cell effector function in MTB-infected lung</td>
</tr>
<tr>
<td>71</td>
<td>Kueht, Michael</td>
<td>University of Texas Medical Branch</td>
<td>Obesity does not result in altered leukocyte count following thermal injury</td>
</tr>
<tr>
<td>72</td>
<td>Johnson, Jameel</td>
<td>Baylor College of Medicine</td>
<td>Upregulation of PD-L1 expression via TLR-4 signaling in human colonic myofibroblasts</td>
</tr>
<tr>
<td>73</td>
<td>Hartog, Nicholas</td>
<td>Medical College of Wisconsin</td>
<td>Role of regulatory T-cells in B-cell anergy and autoantibody production</td>
</tr>
<tr>
<td>Number</td>
<td>Name</td>
<td>Institution</td>
<td>Title</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------</td>
<td>--------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>74</td>
<td>Chen, Zeming</td>
<td>University of Texas Medical Branch</td>
<td>GROWTH FACTOR RECEPTOR BOUND PROTEIN 2 (GRB2) IS A KEY FACTOR IN MEDIATING ENTRY OF ECOTROPIC RETROVIRUS.</td>
</tr>
<tr>
<td>75</td>
<td>Shelite, Thomas</td>
<td>University of Texas Medical Branch</td>
<td>THE EFFECTS OF TICK SALIVA ON THE DENDRITIC CELL-RICKETTSIA INTERACTION, IN VITRO</td>
</tr>
<tr>
<td>76</td>
<td>Schwab, Chet</td>
<td>University of Texas Medical Branch</td>
<td>PHYLOGENETIC ANALYSIS OF HIV-1 IN GALVESTON, TX</td>
</tr>
<tr>
<td>77</td>
<td>Raj, Sean</td>
<td>New York University School of Medicine</td>
<td>EFFECTS OF SUBTHERAPEUTIC DOSAGES OF ANTIBIOTICS ON EARLY LIFE WEIGHT GAIN OF MICE</td>
</tr>
<tr>
<td>78</td>
<td>Magge, Anil</td>
<td>University of Connecticut School of Medicine</td>
<td>ANALYSIS OF DYE BINDING BY AND MEMBRANE POTENTIAL IN SPORES OF BACILLUS SPECIES</td>
</tr>
<tr>
<td>79</td>
<td>Jenkins, Sarah</td>
<td>University of Texas Health Science Center</td>
<td>BACILLUS ANTHRACIS TRANSLOCATION VIA AN INTRACELLULAR ROUTE OF LUNG EPITHELIAL CELLS</td>
</tr>
<tr>
<td>80</td>
<td>Carlsen, Eric</td>
<td>University of Texas Medical Branch</td>
<td>CORRELATION BETWEEN HOST INFLAMMATORY MEDIATOR PROFILE AND LIKELIHOOD OF DEVELOPING MUCOSAL LEISHMANIASIS IN PERU</td>
</tr>
<tr>
<td>81</td>
<td>Forster, Catherine</td>
<td>Columbia University Medical Center</td>
<td>URINARY NEUTROPHIL GELATINASE ASSOCIATED LIPOCALIN IDENTIFIES TUBULAR DISEASE IN HIVAN</td>
</tr>
</tbody>
</table>
50th Annual NSRF
Neuroscience
Poster Session 2
Saturday, April 25, 2009
10:00 am
Hilton Foyer

82 **Given, Shelly**  
*Brody School of Medicine at East Carolina University*  
MINIMAL LOSS OF AUDITORY AND VESTIBULAR FUNCTION IN COCH KNOCK-MICE

83 **dela Cruz, Adriane**  
*University of Texas Medical Branch*  
MOLECULAR MECHANISMS UNDERLYING EARLY COCAINE MEMORIES

84 **Suarez-Delgado, Lorena**  
*University of Nebraska Medical Center*  
NEUROPROTECTIVE EFFECT OF PEROXIREDOXIN 6 AGAINST HYPOXIA-RETINAL GANGLION CELL DAMAGE

85 **Shields-Johnson, Maria**  
*Texas A&M University-Corpus Christi*  
EFFECTS OF LONG-TERM SENSITIZATION ON BITING BEHAVIOR IN APLYSIA CALIFORNICA

86 **Roland, Jarod**  
*Washington University School of Medicine*  
AN EVALUATION OF THE EFFECT OF AGE ON HUMAN MOTOR CORTICAL ELECTROPHYSIOLOGY

87 **Morin, Valérie**  
*Université Laval*  
CEREBRAL FUNCTIONING IN CHILDREN WITH ADHD UNDER ATOMOXETINE TREATMENT

88 **Ju, Xiaoxi**  
*University of Texas Medical Branch*  
DISSECTING FEEDING REGULATING CENTRAL CIRCUITS OF HYPOTHALAMIC MCH NEURONS

89 **Hewlett, Krista**  
*Memorial University*  
EVIDENCE OF ALTERED PSYCHOSOCIAL BEHAVIOR AND COMPROMISED STRESS RESPONSE FOLLOWING ‘MINOR’ STROKE IN THE RAT

90 **Queen, Michael**  
*Louisiana State University Health Sciences Center - New Orleans*  
NEUROTROPHINS REGULATE INFLAMMATORY SIGNALING THROUGH NEUROPROTECTIN D1 IN HUMAN RPE CELLS

91 **Ertel, Monica**  
*Louisiana State University Health Science Center New Orleans*  
THE EFFECTS OF NEUROPROTECTIN D1 (NPD1) ON LASER-INDUCED CHOROIDAL NEOVASCULARIZATION (CNV)
50th Annual NSRF
Oncology
Poster Session 2
Saturday, April 25, 2009
10:00 am
Hilton Foyer

92 Gorgulu, Kivanc
Celal Bayar University Medical School, Manisa - Turkey
ANALYSIS OF TOBACCO MOSAIC VIRUS(TMV) ON PRIMARY AND METASTATIC HUMAN COLON CANCER CELLS TREATED WITH A-LACTALBUMIN OR SULINDAC

93 Coffey, David
University of Colorado Denver
MECHANISMS FOR THE DOWN-REGULATION OF MICRORNA-137 IN MELANOMA

94 Lan, Zheng
University of Cincinnati
OVEREXPRESSION OF EYES ABSENT HOMOLOGY 4 (EYA 4) IN MALIGNANT PERIPHERAL NERVE SHEATH TUMOR CELLS ALTERS THE RETINAL DETERMINATION TRANSCRIPTION COMPLEX AND PROMOTES TUMORIGENESIS

95 Johnson, Timothy
Emory University School of Medicine
LOW-FAT DIET REDUCES THE PROGRESSION OF PREVIOUSLY ESTABLISHED BONE METASTASES IN MICE

96 Barlow, LaMont
Columbia University College of Physicians and Surgeons
PREDICTING RECURRENCE AFTER RADICAL PROSTATECTOMY: DOES AGE MATTER (AND WHEN)?

97 DiNardo, Laura
University of Pennsylvania
PI-103 AND RAPAMYCIN SYNERGISM ABROGATE RESISTANCE TO mTOR INHIBITION IN PRE-B ALL
50th Annual NSRF
Pathology
Poster Session 2
Saturday, April 25, 2009
10:00 am
Hilton Foyer

100  **Raza, Sajjad**
*Dow University of Health Sciences, Karachi, Pakistan*
VARIATIONS IN PRESENTATION OF CELIAC DISEASE IN ADULTS AND ITS ASSOCIATION WITH OTHER CONDITIONS.

101  **Rushing, Natasha**
*University of Tennessee Health Science Center College of Medicine*
PRE-MICROALBUMINURIA AS A NOVEL CARDIOMETABOLIC RISK CORRELATE

102  **Humble, Robert**
*University of Mississippi Medical Center*
DIABETIC GASTROPARESIS – DO DELAYED DIABETICS DIE DIFFERENTIALLY?

98   **Brenneman, Joanna**
*University of Cincinnati College of Medicine*
CHARACTERIZATION OF SIGNALING PROPERTIES OF THE HCMV-ENCODED G PROTEIN COUPLED RECEPTOR US28 AND ANALYSIS OF CONTRIBUTION TO VIRAL INDUCED ATHEROSCLEROSIS

99   **Zhou, Yang**
*University of Texas Health Science Center at Houston*
GENETIC REMOVAL OF THE A2B ADENOSINE RECEPTOR FROM ADENOSINE DEAMINASE-DEFICIENT MICE LEADS TO ENHANCED PULMONARY INFLAMMATION AND FIBROSIS
50th Annual NSRF
Pharmacology and Toxicology
Poster Session 2
Saturday, April 25, 2009
10:00 am
Hilton Foyer

103 **Gipson, Kevin**
*LSU School of Medicine at New Orleans*
THE ANTIANGIOGENIC EFFECTS OF THE METRONOMIC DOSING OF SWEET LEAF TEA

104 **Brownson, Kirstyn**
*Loyola University Chicago, Stritch School of Medicine*
STRONTIUM: A NOVEL TREATMENT FOR BINGE ALCOHOL-INDUCED OSTEOPOROSIS?

105 **Srinivasan, Subhashini**
*University of Illinois, Chicago*
CANGRELOR (ARC69931MX) INCREASES HUMAN PLATELET cAMP LEVELS THROUGH AN ADP-P2Y12INDEPENDENT MECHANISM

106 **Oberoi, Hardeep**
*University of Nebraska Medical Center*
POLYMER MICELLES WITH CROSS-LINKED IONIC CORES AS CARRIERS FOR ANTICANCER AGENT CISPLATIN

107 **Davarian, Ali**
*Golestan Cardiovascular Research Centre, Faculty of Medicine*
ROLE OF CORTISOLE IN ISCHEMIC PRECONDITIONING: NEW EVIDENCES
A-1
THE EFFECT OF HIGHLY PURIFIED CAPSAICIN ON NORMAL ARTICULAR CARTILAGE AND ROTATOR CUFF TENDON HEALING: AN IN VIVO RABBIT STUDY
Rush University Medical Center

Background: Intra-articular bupivacaine infusion, used as an analgesic for arthroscopic orthopaedic surgery, can lead to chondrolysis and potentially impair tendon healing. Therefore, an alternative solution is necessary for post-operative pain. Objective: We utilized an in vivo rabbit rotator cuff (RC) repair model to evaluate effects of highly purified capsaicin on supraspinatus tendon healing and normal glenohumeral articular cartilage. Methods: Skeletally mature, New Zealand White rabbits were randomized to one of four groups: capsaicin injection onto an intact rotator cuff (I+C), unilateral supraspinatus transection and repair with a single 1mL injection into the glenohumeral joint (GHJ) of saline (R+S), placebo (PEG 300) (R+P), or capsaicin (R+C). Contralateral shoulders (Sham) received surgical exposure of the RC but no tendon injury or injection. Animals were euthanized at 18 weeks post-op for assessment of humeral head articular cartilage (proteoglycan (PG) synthesis and content), cell viability, histologic assays) and supraspinatus tendon (biomechanical properties). Results: Maximum load to failure for the supraspinatus was significantly higher (p<0.001) for both I+C (403±72N) and Sham (355±55N), compared to R+S (279±53N), R+P (282±77N), and R+C (263±63N). Cartilage cell viability, computed as live cells/total cells normalized to the viability of the contralateral sham shoulder, was 105±5.5%, 100±7.3%, 102±4.4%, and 102±13%, for I+C, R+S, R+P, and R+C, respectively; no difference between treatment groups (p=0.7). No differences were seen between groups for chondrocyte PG synthesis (p=0.6) and total PG content (0.3). Histologic appearance of humeral heads exposed to different treatment groups was similar (histopathologic scoring, p=0.6), with an intact articular surface, normal safranin-O staining and cellularity. Conclusions: Eighteen weeks following surgery, failure strength of repaired shoulders, irrespective of treatment, was similar, suggesting that capsaicin does not have detrimental effects on the quality of tendon healing. Similarities in cartilage cell viability and metabolic activity across groups suggest that capsaicin does not cause permanent damage to chondrocytes or matrix. Previous rabbit studies have demonstrated bupivacaine toxicity in GH cartilage. In contrast, the current results indicate that, 18 weeks following injection of highly purified capsaicin, RC tendon healing and cartilage metabolism are not compromised.

A-2
ATYPICAL FEMORAL FRACTURES ASSOCIATED WITH LONG-TERM BISPHOSPHONATE TREATMENT
Ding, Anthony, Ioannis Zouzias, Elizabeth Shane, Melvin P. Rosenwasser
Department of Orthopaedic Surgery, Columbia University College of Physicians and Surgeons
Department of Medicine, Columbia University College of Physicians and Surgeons

Background: Hip fractures have a profound impact on the health and welfare of the elderly population. The bisphosphonate drugs are first-line treatment for osteoporosis because they prevent bone loss and promote bone mineralization. However, recent reports suggest that long-term bisphosphonate treatment, while shown to prevent osteoporosis-related fractures, may actually be responsible for causing an atypical fracture pattern of the femoral shaft, unexplained by osteoporosis fragility alone. Osteoporosis-related fractures are spiral comminuted fractures, commonly at the femoral neck and intertrochanteric regions. In contrast, this atypical pattern consists of a transverse, non-comminuted subtrochanteric fracture, associated with diffuse cortical hypertrophy. These fractures can occur without any history of trauma. Moreover, subtrochanteric fractures are highly unstable, prone to deformity and malunion, and thus challenging to treat. Despite widespread concern, little is known about how or why these fractures occur. How long-term bisphosphonate therapy alters the structural properties of the proximal femur has not been investigated, yet that knowledge is crucial to understanding and preventing this phenomenon. Objective: We have taken a unique approach to evaluate the long-term effects of bisphosphonate therapy on the biomechanics of the proximal femur. Methods: Ours is a retrospective longitudinal study using the well-established Hip Structural Analysis program to extrapolate structural properties from serial DXA scan images. Significant parameters included section modulus and buckling ratio, indices of bending strength and local instability. The study population consisted of postmenopausal women diagnosed with primary osteoporosis who have taken oral bisphosphonates for at least 3 years. Results: Our results show that treatment initially improves mechanical strength and stability in the proximal femur. However, after 4-5 years of therapy, both strength and stability decline, especially at the femoral shaft. In contrast, the clinical benefits persisted in the controls treated with either raloxifene or hormone replacement. While these findings support our hypothesis that long-term bisphosphonate treatment negatively alters hip structure, the magnitude of this effect does not fully account for this clinical phenomenon. Future studies may elucidate additional mechanisms contributing to the development of these atypical fractures.
Background - Open fractures are common and devastating injuries that can lead to significant clinical problems. Open fractures are extremely challenging due to bone loss, contamination, and soft tissue damage. Current treatment options have significant complications and unsatisfactory success rates in the prevention and treatment of infection. The best current treatment for contamination is a non-biodegradable antibiotic PMMA beads. These beads produce a high local concentration of antibiotic but avoid toxic systemic levels. Disadvantages of the PMMA beads include the need for surgical removal after use and lack of structural support. A novel approach to improve open fracture outcomes includes the use of a biodegradable, load-bearing scaffold as a delivery vehicle for osteoinductive molecules. The next step is to combine this technique with a way to deliver high local concentration antibiotics to decrease the infection rate in high grade open fractures. Objective - We used a biodegradable, load-bearing scaffold to deliver BMP and varying doses of Gentamicin to promote boney healing across a segmental bone defect and decrease the occurrence of osteomyelitis. We hypothesized that increasing local concentrations of Gentamicin delivered via a biodegradable bone scaffold would show decreasing rates of osteomyelitis in an infected open fracture model in rats. Methods - 5mm defects were created in the right femur of 32 rats. The fracture site was surgically opened and inoculated with S. aureus and E. coli. A load-bearing biodegradable scaffold of polypropylene fumarate (PPF) was surgically placed in the defect and loaded with 10µg BMP. On the scaffold, the control group received no gentamicin (n=10), a low dose group received 10mg gentamicin (n=12), and a high dose group received 20mg gentamicin (n=10). In vivo radiographs were obtained at weeks 1, 3, and 6 and analyzed for evidence of osteomyelitis and fracture gap healing. Results - By 6 weeks, low dose gentamicin rats showed a 50% infection rate and 58% showed gap healing. In contrast, the control had infection and callus formation rates of 90% and 20%, respectively. High dose rats showed an intermediate level of infection and callus formation at 60% and 40%, respectively. Conclusion - This study has shown that a biodegradable, load-bearing scaffold can act as an effective strategy for delivery of both biologically active proteins and concentrated local antibiotics.

TENSILE PROPERTIES OF THE SIMIAN INFERIOR GLENOHUMERAL LIGAMENT
Cassilly, Ryan, Brian Jin, Anuli N. Mkparu, Christopher S. Ahmad, Louis U. Bigliani, Thomas R. Gardner, William N. Levine
(1) Centers of Orthopaedic Research and Shoulder, Elbow and Sports Medicine, Department of Orthopaedic Surgery, Columbia University, New York, NY; (2) Albert Einstein College of Medicine, Yeshiva University, New York, NY; (3) Duke University School of Medicine, Duke University, Durham, NC

Background: The need for an animal model of the shoulder is well established in the literature. The small size of the rodent model makes it difficult to replicate commonly performed shoulder procedures. Anatomical analyses of simian and human shoulders have shown similar musculature and bony structures. However, comparative biomechanical studies of the simian and human glenohumeral joint (GHJ) are lacking. The inferior glenohumeral ligament (IGHL) serves as the primary restraint against anterior instability in the clinical position of apprehension, and several studies have been performed on the human IGHL to determine its tensile properties. Objective: The goal of this study is to determine the tensile properties of the three segments of the simian IGHL (superior band-SB; anterior axillary pouch- AP; posterior axillary pouch- PP) to compare with human shoulder biomechanical properties. Methods: Fresh frozen cynomolugus macaque monkey shoulders (seven female, four male, five left, six right) were dissected down to the GHJ capsule. The IGHL was sectioned into the SB, AP, and PP regions, creating bone-ligament-bone (BLB) specimens as reported in the literature. The initial length, width, and thickness were calculated based on the mean value of multiple measurements using a digital camera and image processing software. The BLB complexes were subjected to a constant ramp displacement of 0.04 mm/sec to failure in uniaxial tension. Two curve-fitting methods (linear regression, exponential stress-strain law) were used to assess regional ligament stiffness. Results: There was no significant difference in length, width, or thickness between the three regions. Failure stresses for the SB (4.7 MPa ± 2.2), AP (4.5 MPa ± 2.7), and PP (4.7 MPa ± 1.6) were not statistically different but were comparable to published human values. The PP trended toward a higher failure strain (35% ± 13) when compared to the SB (23% ± 8), AP (31% ± 11), and human values, while the SB and AP were similar to human data. The SB trended toward being stiffer than the AP and PP. Conclusions: The macaque IGHL demonstrated biomechanical properties similar to that of the human, including similar variations between the SB, AP, and PP. These findings support the establishment of the simian shoulder as a valid model of the human shoulder. Laxity testing of intact simian shoulders is planned to determine if this similarity extends to the response of the simian shoulder to multidirectional loading.
A-5
INTRAOPERATIVE HEMODYNAMIC STABILITY OF PATIENTS DURING BIVENTRICULAR PACING AFTER CARDIAC SURGERY: RESULTS FROM THE BIPACS TRIAL
Spotnitz, Matthew, Marc Richmond, T. Alexander Quinn, Daniel Y. Wang, Santos E. Cabreriza, Henry M. Spotnitz Columbia University College of Physicians and Surgeons

Background: Biventricular pacing (BiVP) improves hemodynamics in select patients with advanced heart failure. However, its role in low output states after cardiac surgery is uncertain. Intraoperative optimization of critical BiVP parameters, including interventricular pacing delay (VVD), may increase BiVP benefits. The Biventricular Pacing after Cardiac Surgery (BiPACS) trial examines the effects of optimized temporary BiVP in cardiac surgery patients with preoperative heart failure and left ventricular (LV) dysfunction. VVD is optimized immediately following separation from cardiopulmonary bypass (CPB). During BiVP optimization, patients are clinically stable, but hemodynamic stability has not been objectively analyzed. Objective: To assess stability of cardiac output (CO), mean arterial pressure (MAP), and systemic vascular resistance (SVR) during intraoperative optimization of VVD. Methods: With informed consent, 7 patients undergoing coronary artery bypass and/or valve surgery with LV ejection fraction = 40% and QRS duration = 100 msec were enrolled. BiVP was implemented immediately after CPB. With optimal atrioventricular pacing delay and epicardial LV pacing site, VVD was optimized in randomized sequence using 10 sec testing intervals over 180 seconds. Median sternotomy in all patients allowed aortic flow measurement with an electromagnetic flow probe. MAP was measured with a radial artery monitor. For each VVD, CO and MAP were calculated by integrating the data over the testing interval. SVR was calculated as SVR=MAP/CO. Vasoactive medications and fluid dosing were kept constant during testing. The slopes of CO, MAP, and SVR vs. time were determined for each patient by linear regression. The slopes were used to calculate change as a percentage of the average value over the entire testing period. Wilcoxon analysis was used to test whether parameters changed by more than 5% vs. the mean during the testing interval. Results: Over 150 180 seconds of testing, there was on average a 5.7±2.3 (SEM)% decrease in CO, a 2.5±1.5% decrease in MAP, and a 3.1±3.4% increase in SVR. Only the change in CO was statistically greater than 5% (p = 0.043). Conclusion: While the BiPACS protocol has been safe clinically, objective criteria of stability should be incorporated. Thus, testing in individual patients should be discontinued if CO decreases more than 15% or if MAP falls more than 10 mm Hg during testing.

A-6
INKJET-BASED BIO-PRINTING OF BONE MORPHOGENETIC PROTEIN AND NOGGIN TO SPATIALLY CONTROL BONE FORMATION IN VIVO
Bykowski, Michael, Greg Cooper, Eric Miller, Emily Lensie, Gary DeCesare, Arvydas Usas, Johnny Huard, Lee Weiss, Joseph Losee, Phil Campbell
Departments of Pediatric Plastic Surgery and Orthopedic Surgery, University of Pittsburgh and Institute of Complex Engineered Systems and The Robotics Institute, Carnegie Mellon University

BACKGROUND: Three-dimensional control of tissue engineering can enable substantial improvements in reconstruction of complex tissue structure abnormalities - for example, those that may occur following trauma, surgical intervention, or congenital malformation. Biological spatial patterning of growth factors plays a critical role directing cell fate during embryo development and wound healing. The capability to engineer specified and persistent spatial patterns of endogenous growth factors within biologically-relevant substrates would be useful to create and sculpt a desired tissue type with a precise shape. In pursuing this goal, we mimicked the pericellular microenvironment present during endogenous bone healing with the ultimate goal of spatially controlling bone formation. We developed a custom-built bio-printing system based on inkjet technology to precisely deposit and physically immobilize growth factors onto physiologically-relevant substrates. Growth factors are immobilized using their native binding affinities for extracellular matrix proteins. OBJECTIVE: The goal of this study was to evaluate the use of bio-printed bone morphogenetic protein (BMP2) and Noggin - well-known, respectively, as osteogenic and osteoinhibitory factors - to spatially control bone formation in vivo. METHODS: Circular bone defects (5 mm) were made in the calvarial bone of adult male mice (n=40). A 5 mm circular piece of acellular dermal matrix - printed with BMP2 (35 ng/implant) on one half and printed with Noggin (35 ng/implant) or untreated on the other half - was implanted in the defect, under the skin. After 4 weeks, cranial defect healing was quantitatively and qualitatively assessed through the use of 3D-CT, radiography, and histology. RESULTS: Within the defect, bone formation occurred in spatial register with the BMP-2 pattern applied. The area of bone formation on the BMP2-treated sides was significantly larger than untreated sides and sides treated with Noggin (both p’s<0.01). Qualitative µCT and histological analyses showed that more new bone formed on the side of the defect treated with BMP2. CONCLUSIONS: Treatment of calvarial defects with bio-printed BMP2 stimulates spatially controlled bone repair. We envision this technology fostering novel techniques for 3-dimensional spatial control of tissue regeneration and that this technology may represent significant advancement in tissue engineering and regenerative medicine.
B-1
IMPACT OF LOWER EXTREMITY PERFORMANCE ON HEALTH-RELATED QUALITY OF LIFE IN OLDER MEXICAN AMERICANS
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Background: Reports from clinical and epidemiological research show that Lower Extremity Performance (LEP) is a significant factor in predicting disability and mortality as compared with upper extremity performance. However, there is no longitudinal examination of LEP impact on health-related quality of life (HRQoL) in older adults. Objective: To examine the association between LEP and both physical and mental HRQoL in older Mexican Americans, one of the fastest growing ethnic groups in the United States. Methods: We conducted a longitudinal analysis using three waves from the Hispanic Established Population for the Epidemiological Study of the Elderly (2000-2006). LEP was measured by the Short Physical Performance Battery (SPPB). HRQoL was assessed by 36-item health survey (SF-36), which creates a physical component summary (PCS) score and a mental component summary (MCS) score. Associations were determined by mixed and Generalized Estimating Equations (GEE) models, adjusting for baseline sociodemographic factors, medical conditions, total body muscle strength, depressive symptoms, and body mass index. This study conforms to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines. Results: At baseline (n= 621), the sample was 59.9% female with a mean age of 78.1 (SD = 5.1) years. Subjects with the best LEP (SPPB score > 9) had significantly higher PCS and MCS scores, respectively, at each wave. Adjusted mixed models revealed that there was a positive association between SPPB and physical HRQoL (Estimate= 1.5, SE= 0.07, p < 0.001) and MCS HRQoL (Estimate= 0.42, SE= 0.06, p < .001), respectively. Moreover, the adjusted odds ratio (OR) of having better physical and mental HRQoL, across time and as a function of best LEP, were 3.77 (95 % CI= 2.73-5.21) and 2.56 (95 % CI= 1.92-3.40), respectively. Conclusions: To the authors’ knowledge, this is the first published report on examining longitudinally the association between lower extremity performance and HRQoL in older subjects. This study provides valuable information that the best LEP is significantly associated with both better physical and mental HRQoL. These findings are relevant to the goal of the Healthy People 2010 initiative of increasing the quality of life for older subjects.

B- 2
PREVALENCE AND EFFECT ON DISEASE SEVERITY OF HEPATITIS D IN HEPATITIS B SURFACE ANTIGEN POSITIVE PATIENTS.
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Background: There is a global decline in the prevalence of hepatitis D infection. However there are still pockets of high prevalence in Pakistan. Objective: The aim of our study was to estimate the prevalence of hepatitis D in HBsAg (hepatitis B surface antigen) positive patients visiting liver clinics in Pakistan and its outcome on disease severity. Methods: The patients who visited the two liver clinics, one in Karachi and the other in Jacobabad, from October 2007 to March 2008, having positive HBsAg, were included in the study. These patients were tested for HBeAg, HBV DNA by PCR, anti-HDV and HDV RNA by PCR. Clinical status of the patients was evaluated by examination, routine biochemical tests and ultrasound. Results: Total number of patients included in the study was 362 comprising of 151 patients from the clinic in Jacobabad and 211 from Karachi. The patients ranged from 4 to 70 years of age (mean age 29.75 ±11.27). Out of the total patients 297 (82%) were male. All the patients were screened for HDV antibody out of which 212 (58.6%) tested positive for the antibody. Total 65 anti-HDV positive patients were tested for the HDV RNA by PCR out of which 30 (46.2%) tested positive for the virus. Three hundred and forty (340) patients were screened for HBeAg out of which 71 (20.9%) tested positive for HBeAg. Three hundred and seven patients were screened for HBV DNA by PCR out of which 88 (28.7%) tested positive for the virus. HBV DNA was positive in 16.2% of HBeAg negative patients (pre-core mutants). The frequency of positive HDV antibody was 69.23% in patients from Kashmore, 67% in Jacobabad, 65.4% in Jaffarabad, 65.21% in Quetta, 60% in Naseerabad, 36.58% in Karachi, 58.33% in other areas of Balochistan and 60.71% in other areas of Sindh. Of the total patients visiting the clinics 284 (78.5%) were clinically non-cirrhotic and 78 (21.5%) were cirrhotic comprising of 44 (12.2%) patients with de-compensated cirrhosis and 34 (9.4%) with compensated cirrhosis. Positive HDV antibody status was associated with more severe and advanced disease (p=0.000). Conclusion: This data show extremely high prevalence of hepatitis D in the referred patients from some areas of Pakistan. Presence of HDV antibody is associated with more severe and advanced form of the disease. HBsAg positive patients visiting liver clinics should also be routinely screened for HDV antibody. Pakistan may be considered as the area of highest HDV prevalence around the globe.
THE EFFECT OF MEDICAL CONDITIONS ON ACTIVITY LIMITATIONS IN OLDER MEXICAN-AMERICANS

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BACKGROUND: The presence of chronic conditions in old age is associated with functional limitations and disability (Verbrugge et al., 1991). Obesity has been associated with several prevalent chronic conditions in older people (Bray, 2004). However, the association between obesity and functional disability among older Hispanic Americans has not been given much attention in the literature as it has in the general population (Soham et al., 2005). These research gaps are critical since obesity has serious health consequences including the development of chronic conditions. OBJECTIVE: The objective of this study is to examine the effect of obesity and chronic conditions on the functional limitations in older Mexican Americans. It is especially expected that obesity would be associated with lower body function and morbidity. The present analysis used data on Mexican Americans aged 75 and over using data from wave 5 of the Hispanic Established Population for the Epidemiological Study of the Elderly (H-EPESE) which were collected during 2004-2005. METHODS: I use data from the H-EPESE Wave 5 having been conducted in 5 southwestern states (Arizona, California, Colorado, New Mexico, and Texas) beginning in 1993. Wave 5 data were collected during 2004 and 2005. 1167 subjects now aged 75 and over were interviewed. A representative sample of 902 Mexican Americans of the same age were added going a total of 2069 subjects. Measures include medical conditions, Body Mass Index (BMI), activities of daily living (ADL), and socio-demographic information. RESULTS: Logistic regression is used in the analysis of functional limitation indicators on age, gender, selected chronic diseases, and obesity. Higher obesity (more than 30 BMI) is only the impairment of walking across small room (1.503), any ADL limitation (1.720), stairs of 2nd floor (1.549), and walk 1/2 mile (2.013) compared with normal BMI people. Every missing BMI cases are highly significant for all models. CONCLUSIONS: This study find obesity is a kind of explanation of physical impairments with chronic diseases especially in walking and transferring. A limitation in this study is conducted as a cross-sectional research design although H-EPESE is longitudinal data set. In sum, this study is found the effect of obesity and chronic diseases on the functional limitations in older Hispanic-American using H-EPESE data.

EFFECT OF LAPAROSCOPIC ADJUSTABLE GASTRIC BANDING (LAGB) ON METABOLIC SYNDROME & ITS RISK FACTORS IN MORBIDLY OBESE ADOLESCENTS

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Background: While the prevalence of U.S. adolescent obesity and obesity-related comorbidities are increasing at an alarming rate, current non-invasive efforts at weight loss show disappointing long-term results. Increasing evidence suggests that Laparoscopic Adjustable Gastric Banding (LAGB) in adolescents is a safe and effective method of sustainable weight loss. Although bariatric surgery has been shown in adults to be effective in improving parameters of, or even reversing, Metabolic Syndrome (MeS), to the best of our knowledge this has not yet been investigated in a pediatric population. Our aim thus was to evaluate the effect of LAGB on inflammatory markers and components of MeS in morbidly obese adolescents. METHODS: Data was obtained in 24 multiethnic adolescents (9M, 15F, 16.4 ± 1.2 yrs) enrolled in an IRB approved LAGB program. All procedures were performed by a single surgeon. Anthropometric and metabolic data was analyzed and compared prior to, 6 mo and 12 mo post-LAGB. Twenty-four adolescents had 6 mo post-LAGB data and twelve had data through 12 mo. MeS was defined by the Cook criteria. RESULTS: At baseline, 13/24 met criteria for MeS. At 6 mo, there were significant changes in BMI from 51.3 ± 11.3 kg/m2 to 46.2 ± 11.7 kg/m2 (p<.0000004), Waist Circumference (WC) from 141 ± 19.9 cm to 131.2 ± 21.6 cm (p<.0008), TG from 127 ± 64.5 mg/dl to 100 ± 43.5 mg/dl (p<.0098), Systolic BP percentile from 71.3 ± 28.6% to 55.3 ± 31.6% (p<.02) and CRP from 8.9 ± 10.1 mg/L to 5.7 ± 7.8 mg/L (p<.001). The prevalence of MeS dropped from 54.2% to 29.2%. In our 12 mo cohort, there were significant changes in BMI from 48.0 ± 7.6 kg/m2 at baseline to 42.0 ± 8.3 kg/m2 (p<.0003) 12 mo post LAGB, WC from 135.9 ± 15.4 cm to 125.3 ± 17.7 cm (p<.013), and CRP from 6.0 ± 4.6 mg/L to 2.8 ± 2.6 mg/L (p<.0055). The prevalence of MeS dropped from 41.7% to 16.7%. Rapid improvement in MeS parameters occurred during the first 6 mo with continued but less dramatic changes to 12 mo. CONCLUSION: LAGB effectively improves components of MeS as well as inflammatory markers in morbidly obese adolescents. Although long-term studies are necessary, LAGB may be a useful intervention for refractory morbid obesity to decrease early development of comorbidities and cardiovascular adverse events in this young population.
TEMPORAL TRENDS IN STROKE CARE IN THE UNITED STATES, 1998 - 2006

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Background: The prevention and treatment of stroke has changed in the past decade. However, national data on in-hospital stroke care has not been explored in the literature to date. Objective: We utilized the Nationwide Inpatient Sample (NIS), an annual administrative dataset of 20% of all hospitalizations in the United States, to quantify changes in stroke incidence and care over time. Methods: Stroke hospitalizations in NIS datasets from 1998 to 2006, the most recent dataset, were identified by searching diagnoses for ICD-9 codes associated with acute ischemic stroke. Annual counts of stroke hospitalizations, tabulated by patient and hospital characteristics, were calculated. Linear regression was performed on temporal trends. In-hospital mortality in the course of stroke hospitalization was modeled by multivariate logistic regression as a function of patient characteristics (age, gender, race, comorbidities), hospital characteristics (size, region, location, status as a teaching hospital, annual stroke case-load), and characteristics of the hospitalization (year, length-of-stay, cost). Results: From 1998 to 2006, the number of stroke hospitalizations decreased 14%, a statistically significantly trend (p for slope <0.0001). Among races, the number of stroke hospitalizations decreased significantly among `white' race (p<0.0001), but not among those of `black', `other', and `missing' race groups. There was a 1% absolute decrease in in-hospital mortality for stroke from 1998 to 2006, a statistically significant trend (p = 0.0003). In multivariate analysis, female gender, geographic region, hospitalization in a teaching hospital, and increasing age, comorbidity score, and cost of hospitalization were associated with significantly greater odds of in-hospital mortality following stroke hospitalization. Factors associated with significantly reduced odds of death were: race, urban hospital location, increased annual hospital stroke caseload, length-of-stay beyond one day, and hospitalization for stroke from 2002 onwards. Conclusions: Stroke prevention and care improved between 1998 and 2006, but disparities exist.

ON SPONGE-GRAFTING: REDISCOVERY OF A HISTORICAL PLASTIC SURGERY TECHNIQUE

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Background: In the early 1880s general surgeons began to experiment with skin grafts, tissue grafting, flaps and other modern-day plastic surgery techniques. Without a knowledge of tissue histology and immunological reaction, many of these grafts failed. The problem of deeply eroded ulcers and large traumatic defects continued to elude surgeons: how could tissue be built up? Scottish surgeon David Hamilton proposed sponge-grafting. Objective: The purpose of this paper was to investigate the development and dissemination of the technique of sponge-grafting, as well as to describe case reports of its success or failure. Contemporary practitioners' understanding of the science behind the technique (particularly "what became of the sponge?") was also studied. Methods: Primary sources, drawn from the British, American, Australian and Canadian medical and surgical literature of the late 19th century, were exhaustively reviewed. Forty-five articles, book chapters, and case reports of sponge-grafting from the 1880s-1900s were found. A detailed comparison of practitioner technique, success and medical understanding for why sponge-grafting succeeded where allografted tissue failed was also undertaken. No secondary literature appears to exist on sponge-grafting. Results: Sponge-grafting was a remarkably successful technique; over 80% of case reports reported a positive outcome (including ulcer regression, traumatic defect repair, syphilitic chancre regression, artificial eye placement and burn coverage). There was little variation in surgeons' preparation and application of the sponge. Pathological examination of grafted sponge revealed inosculating blood vessels and granulation tissue along with lymphocytic infiltrates, which were often interpreted according to the modern understanding of these findings --though many other surgeons thought the sponge itself, as a living animal, was generating the new blood supply and tissue bed. Conclusions: Surgeons of the day were keen observationalists and applied a new technique without seeing it demonstrated. Sponge-grafting was a successful means of covering difficult, indolently healing, or disfiguring wounds and sparked investigation into histocompatibility and inflammation. This paper is the first to describe the technique of sponge-grafting in the modern literature and notes that no similar mechanism of building up tissue defects via exogenous, absorbable material exists today in plastic surgery.
INTRODUCTION: Waiting for health care services is common in publicly funded national health services. Timely access to care has become a primary concern for most Canadians and lengthy queues are threatening to destabilize Medicare. Centralization of wait lists through the use of common referral systems has been suggested as a means of decreasing variability in wait times, improving equality in access to care and efficiency of health care delivery, and providing sustained reductions in wait times.  

OBJECTIVE: The purpose of this study was to determine if evidence existed to support implementation of a common referral system, the impact of such a system on wait times, and the acceptability among referring physicians.  

METHODS: A retrospective analysis of wait time data collected on 2383 elective surgical consultations seen by a group of 6 academic general surgeons over a 1 year period was undertaken. Following which a prospective analysis of wait times for 2027 incoming referrals received over a 9 month period following implementation of an optional common referral system was completed. Finally, a survey of 519 referring physicians was undertaken to determine satisfaction with the system.  

RESULTS: Prior to implementation of the common referral system there was significant variability in wait times among patients with the same diagnosis, depending on which surgeon they were referred to. The length of time patients with a hernia waited for surgical consultation varied from a median of 14 days to 188 days, those with benign hepatobiliary disease from 17 to 150 days, and those with benign anorectal disease from 43 to 155 days, while those with malignant disease varied from 12 to 28 days. The 23% of patients who were referred to the common system following its implementation experienced a 48% reduction in wait for surgical consultation. The physician survey yielded a 40% response rate and indicated that those who utilized the common referral system were satisfied with it and that respondents would support an expansion of such an initiative.  

CONCLUSION: The historical practice of individual surgeons maintaining their own wait lists has produced considerable variability in wait times for surgery and inequality in access to care; consequently there may be variability in the severity of need of patients undergoing surgery. It appears that common referral systems may be an acceptable means of improving equality in access to care and efficiency in health care delivery. 

INFANT OBESITY IN PEDIATRIC PRACTICE  

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Background: Previous studies have shown that infants who were in the highest percentiles weight/length at any point between 0-11 months were more likely to become obese during childhood. This study aimed to confirm that the trend towards obesity begins as early as age six months, and to investigate our clinician’s practices regarding diagnosis and treatment of infantile obesity.  

Methods: This was a retrospective nested case-control design using data abstracted from the electronic medical record of patients seen for well-child visits at the UTMB pediatric clinic. Weight/length (W/L) percentiles for age and gender were calculated using a SAS® program from the U.S. Centers for Disease Control. Obesity was defined as = 95 percentile. Obese at 24 month subjects (N=102) were compared with a randomly selected subset (110 of 442) of non-obese subjects aged 24 months.  

Results: Compared with normal subjects aged two years, subjects who were obese at 24 months were more likely to have been obese when aged six months (odds ratio = 13.3). A total of 35% of obese subjects at age 24 months were obese at six months; whereas only 4% of subjects normal at age 24 months were obese at age six months. Only 14% percent of obese infants aged six months were diagnosed with obesity; 24% of these had more than the routine amount of weight control advice. Of obese subjects aged 24 months, 23% were diagnosed obese and 38% of these received more than routine amount of weight control advice.  

Conclusion: Obesity is prevalent among infants and young children in our clinic population. Obesity at age 24 months was highly likely to have been present from age six months. However, clinicians diagnosed obesity for only a minority of children. Counsel regarding obesity was rarely provided at either age.  

Implications: Although obesity at age six months was observed in our practice, and was a strong predictor of obesity at age two years, our clinicians infrequently recorded diagnosis or management of the condition. Primary care providers should begin to recognize obesity in young children with the goals of documenting the prevalence of obesity in their practice and working to develop safe, effective interventions.
Background: Although several studies have shown positive associations between patients' health seeking behaviors and health outcomes, less is known about these relationships in disadvantaged patients. Objective: This study examines the association between patients' interest in seeking health information, using health promotion services, and receiving clinician counseling among a sample of low-income Latino patients. The hypothesis is that patients with high services utilization and proactive health seeking behaviors are more likely than those who are not to receive healthy behavioral lifestyle and disease prevention counseling by clinicians. Methods: An analysis of an interval patient assessment conducted at 4 adult health clinics within the Venice Family Clinic (VFC) system in Los Angeles County was carried out to test the hypothesis. Analysis was focused on data collected from 301 survey respondents who identified themselves as Latinos. Study variables included patients' socio-demographics, health seeking and health promotion services utilization patterns, and reports of receiving clinician counseling on disease prevention and maintaining healthy lifestyle habits, such as nutrition and physical activity. Results: Analysis revealed that out of a list of 14 topics, only 5 topics on health-related information were sought by survey respondents with “managing chronic disease” (58%) and “maintaining healthy weight” (60%) being the most frequent. Also, from a list of 13 available health promotion services in the clinics, an average of 1.4 services per person were used with “reproductive care” (19%) and “prenatal care” (12%) being the most frequent. Patients who acquired greater amounts of health-related information were more likely to use a higher number of services rendered in the clinic (r = 0.31, p < .001). Additionally, a higher number of health promotion services used in the clinic were associated with a greater frequency of communication between patients and clinicians (r = 0.28, p < .001). Better communication with clinicians was also positively correlated with patients receiving more health-related counseling (r = 0.41, P < .001). Conclusions: Clinic-based interventions and strategies to encourage and motivate Latino patients to become more proactive about their health by asking questions and utilizing health promotion services may facilitate patient-centered care and receipt of healthy behavioral lifestyle and disease prevention clinician counseling.

B-10
LINKAGE AND ASSOCIATION MODELING OF CANDIDATE GENES IN NON-SYNDROMIC CLEFT LIP AND PALATE IN THE HONDURAN POPULATION
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BACKGROUND: Cleft lip with or without cleft palate and isolated cleft palate (CLP/I) are common congenital malformations, occurring in 1.5-2/1,000 Caucasian births with a greater incidence in Hispanic, Asian, and Native American populations. Syndromic cases of CLP/I generally follow Mendelian patterns of inheritance, while non-syndromic forms show complex inheritance patterns with reduced penetrance. Multiple candidate genetic loci for non-syndromic cleft lip with or without cleft palate (NSCLP) have been identified through studies of many different populations, but no published studies have examined Hondurans, despite the high prevalence of clefting (approximately 1/500 births). Three genes were examined based on previous reports of positive association with clefting in the literature: SUMO1, PVRL1, and IRF6. Several studies support an association between NSCLP and SNPs in IRF6 across various populations. No SNPs have been previously examined in SUMO1, but it has been associated with NSCLP through a breakpoint mutation in an affected Caucasian girl. One SNP in PVRL1 has been associated with NSCLP in a Guatemalan population. OBJECTIVE: To investigate the genetic influence of 3 candidate genes on NSCLP in a Honduran population. METHODS: We evaluated 13 single nucleotide polymorphisms (SNPs) via linkage and association modeling in pedigrees (LAMP). A set of 5 SNPs in and around IRF6 were tested along with 5 SNPs from SUMO1 and 3 SNPs from PVRL1. Subjects (276 individuals from 59 families) were recruited through a cleft clinic in a Honduran hospital after screening for syndromic markers. Families were required to have 1 member with confirmed NSCLP and at least 2 members affected with clefting by report. RESULTS: Our study was suggestive of linkage for 3 SNPs (rs1856161, rs2235371, and rs2235377) in IRF6 (LODs = 1.97, 1.56, and 1.73, respectively), and found a significant association between them and the disease locus (p = 0.05) in our population. There was no significant association between the disease locus (all p-values > 0.05) and the other examined SNPs. CONCLUSIONS: This study is the first to confirm the association of NSCLP with IRF6 in the Honduran population, supporting the existence of population-independent NSCLP genetic risk factors. However, the lack of significance in SUMO1 and PVRL1 imply that unique genetic risks for NSCLP in groups with different ancestries do still exist. Further study is necessary to identify potential causal variant
CXCR4 is a chemokine receptor which is aberrantly overexpressed on metastatic tumor cells. We have developed an in vitro model system in which non-metastatic MCF7 breast tumor cells overexpress CXCR4 to test the role of CXCR4 signaling on tumor cell recruitment and extravasation. A first and critical step for organ specific recruitment is the capture of circulating tumor cells by the vascular endothelium of tissues that express the CXCR4 ligand, CXCL12. Overexpression of CXCR4 promotes adhesion to extracellular matrix and endothelial ligands. ROCK is a serine/threonine kinase activated by the small GTPase, RhoA, which is associated with a positive effect on integrin adhesions. We hypothesized that one mechanism for promoting invasion and metastasis is by stimulating adhesion through ROCK between circulating tumor cells and the vascular endothelium of distal organs. Interestingly, our results unexpectedly showed an increase in cellular adhesion at early time points when ROCK activity was inhibited with Y-27632. Because cell adhesion is directly related to the formation of individual adhesion complexes, we used TIRF microscopy to observe integrin complexes containing GFP-paxillin during the first 20 minutes of adhesion. In control cells, numerous adhesion complexes formed, resembling those typically found in adherent cells. In cells treated with Y-27632, adhesion complexes still formed, but were smaller and exclusively contained markers of early adhesion complex components. While abnormal, the adhesion complexes which formed in the absence of ROCK activity retained the ability to support cellular adhesion. Thus, we predicted that during initial cell adhesion events, Rho and ROCK activity are transiently decreased to promote the transition from suspension to adhesion. To test the requirement for an initial inhibition of ROCK activity during cell adhesion, we utilized a constitutively active ROCK mutant. Cells expressing constitutively active ROCK effectively blocked cell adhesion in response to CXCL12, supporting the model that ROCK activity must be decreased to promote early cell adhesion events. Finally, we used a flow chamber to introduce physiological shear stress into our experimental system and found that CXCL12 dramatically increased both adhesion and cell spreading. Our results demonstrate that CXCL12/CXCR4 promotes tumor cell capture by decreasing the activation of ROCK and provides a mechanism for organ selectivity during metastasis.

THE ROLE OF MOLECULAR CHAPERONE UNC-45A IN HUMAN BREAST CANCER

Purpose: Breast cancer is the third most common cause of death due to cancer in the United States. Approximately 90% of breast cancer deaths are caused by metastasis to bones, liver, lungs, or brain with a survival time for patients of 2 years. Cancer metastasis is tightly related to cell motility including cell invasion and migration in breast cancer. UNC-45 functions as a molecular chaperone for myosin motors and as a co-chaperone for Hsp90 in both vertebrate and invertebrate animals. The goal of this study is by understanding the molecular interaction of UNC-45A, its protein partner Hsp90, and the target myosin motors, to enhance our ability to develop new molecular strategies for more effective therapy of breast cancer. Methods: We used immunohistochemistry to study the UNC-45A expression patterns in human breast cancer specimens. The UNC-45A mRNA and protein levels were quantified in several human breast cancer cell lines by qRT-PCR and Western Blots. In Vitro cell lines are serving assess the effect of UNC-45A on cell growth, migration, and invasion. Results: Humans and other vertebrates produce two isoforms encoded in separate genes, UNC-45A expressed generally and UNC-45B expressed in heart and skeletal muscle. Humans and other mammals alternatively splice the UNC-45A mRNA to produce two spliceoform proteins, differing by a 15 amino acid-residue, proline-rich sequence near the N-terminus. In human breast cancer patient specimens UNC-45A level is up-regulated dramatically in high grade groups. In metastatic breast cancer cell lines and other cancer cell lines including cervical and colon adenocarcinoma cell lines, the shorter spliceoform is over-expressed. Recombinant human UNC-45A pulls down myosins IIA, IIB and Hsp90 beta, which have been implicated in cell proliferation, migration, and critical processes in cancer metastasis. Future experiments are needed to test whether 1) Knockdown of UNC-45A prevents cancer progression both in vitro, and in vivo. 2) Interactions of UNC-45A, myosinII and Hsp90 are mechanistically linked to the metastatic behavior. Conclusion: Human breast cancer tissues express higher levels of the UNC-45A gene products than normal breast tissues. The later stage tumors express higher levels of the UNC-45A gene products than the early stage tumors. Tumorigenic non-metastatic cell lines (MCF-7, T47D) express higher levels of UNC-45A proteins than non-tumorigenic cell line (HMEC). Tumorigenic metastatic cell line (MDA-MB-231).
C-3

THE ROLE OF β-ARRESTIN2 IN MORPHINE INHIBITION OF EGF-INDUCED PROLIFERATION OF ASTROCYTES

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Astrocytes play an integral role in brain functions such as initiating and sustaining synaptogenesis and modulating neural progenitor cell fate decisions. Astrocytes, like neurons, possess the µ-opioid receptor (MOR), which is a target for morphine. Understanding morphine's effect on astrocytes in brain development can elucidate the pathologies of neurological development in the fetus of a heroin abusing mother. Previous studies revealed that acute treatment (min) of morphine promote a transient, short lasting phosphorylation of ERK/MAP kinase, a cell signaling component implicated in cell proliferation. Moreover, morphine dependent ERK phosphorylation seems to occur through both G protein dependent and non-G protein dependent mechanisms by transactivating the EGF receptor (EGFR), which phosphorylates ERK. The scaffold protein β-arrestin2 also seems to have a role in ERK activation following morphine treatment, but the mechanism has yet to be delineated. Specifically, it is unknown if β-arrestin2 participates in ERK phosphorylation at a step leading to EGFR transactivation, or whether it is involved in a step downstream of EGFR activation. To address the first possibility, we transfected rat astrocytes with β-arrestin2 siRNA and treated them with morphine. Immunoprecipitation of EGFR and western blotting showed a decrease in phospho-EGFR following morphine treatment of cells transfected with β-arrestin2 siRNA compared to morphine treatment in control cells, indicating a role for β-arrestin2 in EGFR transactivation. To address a role for β-arrestin2 downstream of EGFR, we treated β-arrestin2-transfected astrocytes with EGF. Western blot analysis indicated that β-arrestin2 siRNA inhibited EGF-induced ERK phosphorylation. Previous studies have also shown that chronic (h) morphine treatment inhibits EGF-stimulated proliferation of astrocytes via ERK dependent internalization of the EGFR. It is uncertain, however, if β-arrestin2 is involved in this aspect of morphine activity. Using BrdU labeling to measure cell proliferation, we found that astrocytes transfected with β-arrestin2 siRNA and treated with chronic morphine exhibited a reversal in the inhibition of EGF-stimulated proliferation. Taken together, these studies suggest the involvement of β-arrestin2 in two pathways of morphine-influenced astrocyte cell division, the canonical pathway associated with G protein coupled receptors and an unprecedented one involved in EGF signaling.

C-4

COACTIVATOR ASSOCIATED ARGININE METHYLTRANSFERASE CONFERS SUBSTRATE SPECIFICITY FOR O-GLCNAC TRANSFERASE

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Post-translational modification of Ser/Thr residues by β-N-acetylglucosamine (O-GlcNAc) is a ubiquitous and dynamic post-translational modification in metazoans. Many different types of proteins are GlcNAcylated, ranging from signaling molecules, cytoskeletal proteins, proteasomal proteins, to most components of the transcriptional machinery. GlcNAcylated proteins are also phosphorylated, sometimes occurring competitively on the same residues, suggesting a complex and extensive inter-relationship between these two modifications. GlcNAcylation is highly dynamic, responding to a wide variety of stimuli and its dysregulation is implicated in diabetes and neurodegenerative disorders. Unlike phosphorylation, which is controlled by hundreds of different kinases, there is only a single gene encoding the enzyme that catalyzes the addition of O-GlcNAc, O-GlcNAc Transferase (OGT), and a single gene encoding the protein that removes the sugar, O-GlcNAcase. GlcNAcylation is absolutely essential for life as embryonic stem cells harboring the null mutation for OGT are not viable. With the large number of known substrates for OGT, the question we sought to address was what confers substrate specificity for this enzyme? Using a yeast two-hybrid approach, we identified Coactivator Associated Arginine Methyltransferase 1 (CARM1) as an OGT-interacting protein. CARM1 is a coactivator important in nuclear hormone receptor mediated transcription. Here, we demonstrate through immunoprecipitation studies that CARM1 interacts with OGT and is GlcNAcylated in vivo. Incubation of recombinant CARM1 with recombinant OGT and 3[H]-UDP-GlcNAc, the donor sugar for OGT, demonstrated that CARM1 is an in vitro substrate for OGT. Additionally, we show that CARM1 is able to direct OGT to specific substrates in an in vitro assay. Finally, in CARM1-dependent luciferase assays, we show that OGT was able to potentiate CARM1-dependent transcription. Here, we show that a CARM1-OGT complex is able to confer substrate specificity for OGT. However, what we would like to determine is if it is solely the interaction between these proteins that directs OGT to substrates or if OGT specificity is dependent on CARM1 methyltransferase activity. Determining the nature of the interaction between these two proteins could provide molecular insight and possible therapeutic targets for diseases that work through nuclear hormone receptor signaling such as metabolic disorders and cancer.
C-5

CXCR4 REGULATION IN CARDIAC MYOCYTES AFTER HYPOXIC INJURY
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Background: Chemokine receptor 4 (CXCR4) and its ligand, Stromal Derived growth Factor-1(SDF-1) play an important role in the homing of stem cells and preservation of cardiac myocytes at the site of injury. Recent studies have also demonstrated that CXCR4 is expressed in adult cardiac myocytes after myocardial infarction and initiates antiapoptotic signaling via AKT- and ERK-phosphorylation. Also, basic Fibroblast Growth Factor (FGF-2) has been found to mediate cardioprotection following myocardial insult by increasing the myocardial viability post-MI. Objective: We hypothesized that in hypoxic cardiac myocytes, these potential antiapoptotic effects of FGF-2 are mediated via upregulation of SDF-1 receptor, CXCR4. To address this issue, we determined CXCR4 expression in murine neonatal cardiac myocytes under normoxic and hypoxic conditions and monitored its response to different doses of FGF-2. Methods: Cardiac myocytes isolated from neonatal C57BL6 mice. The expression of CXCR4 in neonatal cardiac myocytes was confirmed by immunostaining 2-3 days post isolation. CXCR4 mRNA expression was analyzed by real time RT-PCR using total RNA extracted from the cardiac myocytes. 6 X 10^5 cells were plated in each 60mm plate. The cells were maintained in 15% serum for 48 hours prior to experimental treatments that were carried out in 1% serum-containing media. Results: The results demonstrated 1.5 fold induction of CXCR4 mRNA expression in neonatal cardiac myocytes subjected to 36 hours of hypoxia. Treatment with FGF-2 only for 36 hours also increased the expression around 1.5-2 fold in a dose dependent manner. However, the hypoxia mediated upregulation of CXCR4 mRNA expression was further increased by 3 folds when the cells were treated with 5 ng/ml FGF-2 for 36 hours. Conclusion: This study demonstrates that cardiac myocytes express CXCR4 that is upregulated during hypoxia and in response to FGF-2 and synergistically in response to hypoxia and FGF-2. Taken together, these findings suggest that one mechanism for the benefits of the administration of growth factors like FGF-2 may be due to up-regulation of cardiac myocyte CXCR4 expression and downstream inhibition of cardiac myocyte death.

C-6

A NOVEL ROLE OF Gaz and Gaq SUBUNIT PROTEINS IN CENTRAL a1 AND a2 ADRENERGIC RECEPTOR-MEDIATED CHANGES IN CARDIOVASCULAR AND RENAL FUNCTION IN CONSCIOUS SPRAGUE-DAWLEY RATS
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Background: The diuretic, but not cardiovascular (CV) depressor, responses produced by central activation of Nociceptin/Orphanin FQ receptors - a G-protein coupled receptor (GPCR) - are mediated by Gaz and Gaq subunit protein pathways. Currently the Ga-subunit pathways mediating central a1 and a2 adrenoceptor stimulated cardiorenal responses remain unknown. Objective: To determine the role(s) of brain Gaz/Gaq subunit proteins in mediating the CV and renal responses produced by central a1 and a2 GPCR stimulation. Methods: Male Sprague-Dawley rats were pre-treated centrally (24-h) via an intracerebroventricular (i.c.v.) injection of a Gaz-subunit oligonucleotide (ODN, 25 µg ea.) directed against Gaz or Gaq or a scrambled (SCR) ODN. On the day of study, the femoral artery, vein and bladder were cannulated, and rats were infused with isotonic saline (55 µl/min). After equilibration, heart rate (HR), mean arterial pressure (MAP) and urine output were measured (2.5h, 10-min periods) prior to and post i.c.v. injection of the a1 agonist methoxamine (200 µg) or the a2 agonist guanabenz (50 µg) (N=4/group). Results: I.c.v. methoxamine significantly increased MAP and decreased HR and urine flow rate. In contrast, i.c.v. guanabenz decreased both MAP and HR and produced diuresis. The down-regulation of Gaz or Gaq subunits (confirmed by immunoblotting, 85% down-regulation) did not alter the CV effects post i.c.v. a1 or a2 agonist administration. In contrast to SCR ODN treated rats, in which i.c.v. methoxamine significantly decreased urine flow rate (peak., -43±2 µl/min, 70-min duration) Gaz protein down-regulation significantly enhanced the duration (100-min), but not magnitude, of the antidiuresis. Alternatively, in central Gaz ODN treated rats the antidiuretic response to i.c.v. methoxamine was significantly blunted and of shorter duration (peak., -30±5 µl/min; 50-min duration). In other studies, Gaz protein down-regulation blunted the magnitude/duration of diuresis to i.c.v. guanabenz; whereas the diuresis to central guanabenz was markedly enhanced in peak magnitude (., SCR, 194±16; Gaz ODN, 268±21 µl/min), cumulative output (SCR, 10202±232 µl; Gaz ODN, 16838±369 µl) and duration in Gaz ODN-treated rats. Conclusion: These studies demonstrate that brain Gaz and Gaq protein subunits play physiologically important and selective roles in controlling the pattern of urine output produced by central adrenoceptor activation, presumably by modulating vasopressin secretion.
HIV-2/HIV-1 ENVVELOPE CHIMERAS DETECT HIGH TITER BROADLY REACTIVE HIV-1 V3-SPECIFIC ANTIBODIES IN HUMAN PLASMA

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Background: Identifying the antibody specificities that constrain HIV-1 envelope (Env) diversity, limit virus replication, and contribute to neutralization breadth and potency is an important goal of current HIV/AIDS vaccine research. Here we describe a novel HIV-2 proviral scaffold into which we substituted the complete env V3 region of HIV-1YU2 or HIV-1Ccon to yield the chimeric viruses HIV-2KR.X7YU2 V3 and HIV-2KR.X7Ccon V3. Objective: To characterize the breadth and potency of neutralizing antibody (Nab) reactivity to HIV-1 V3 during natural infection. Methods: HIV-2/HIV-1 V3 chimeras were constructed and tested for biological function and antigenicity against a panel of HIV-1 and HIV-2 Env-specific ligands. V3 specific reactivity was assessed in polyclonal plasma samples obtained from patients infected with clade B and clade C HIV-1. Results: HIV-2/HIV-1 V3 chimeras were found to be infectious, replication competent and sensitive to selective pharmacological inhibitors of virus entry. V3 chimeric viruses were resistant to neutralization by HIV-1 mAbs directed against the CD4 binding site, coreceptor binding site, and MPER but exhibited striking sensitivity to HIV-1 V3 specific mAbs. 447-52D and F425 B4e8 (IC50 < 0.005 g/ml for each). Plasma specimens from 11 HIV-1 clade B and 10 HIV-1 clade C chronically infected subjects showed subjects against HIV-2 but exhibited high titer V3-specific neutralization against both HIV-2/HIV-1 V3 chimeras with IC50 measurements ranging from 1:50 to greater than 1:40,000. Neutralization titers of clade B plasma were found to be as much as 1000-fold lower when tested against the primary HIV-1YU2 virus compared with the HIV-2KR.X7YU2 V3 chimera, demonstrating highly effective shielding of V3 epitopes in the native Env trimer. HIV-2/HIV-1 V3 chimeras were potently neutralized by 14 sera obtained from individuals recently infected by clade C HIV-1, but these titers did not correlate with autologous or heterologous neutralization by the same sera. Conclusions: We conclude that V3 is highly immunogenic in vivo, eliciting antibodies of significant breadth and neutralizing potential during both acute and chronic HIV-1 infection. These antibodies constrain HIV-1 Env to structure(s) in which V3 epitopes are concealed prior to CD4 engagement but they do not otherwise contribute to neutralization breadth and potency against most primary virus strains.

ROLE OF AMNIOTIC FLUID IN REDUCING AND/OR PREVENTING NECROTIZING ENTEROCOLITIS IN EXPERIMENTAL PREMATURE NEONATAL RAT MODEL

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Background: Necrotizing Enterocolitis (NEC), a potentially fatal condition, is the most common gastrointestinal disease of premature infants & affects 5-10% of premature neonates. The exact etiology of NEC is not known, but prematurity, formula feeding, intestinal ischemia, bacterial colonization, and decreased GI motility are associated with NEC. A leading hypothesis involves an exaggerated inflammatory response mounted by immature intestinal epithelial cells in response to gastrointestinal injury. Objective: We studied the role of amniotic fluid (AF) in reducing and/or preventing NEC in a rodent NEC model and the potential that hepatocyte growth factor plays a key role. Methods: We retrieved AF from 18 day pregnant Sprague Dawley rats and measured HGF and EGF concentrations by ELISA. IEC-6 and RIE rat intestine epithelial cells were exposed to different concentrations of AF (0, 10, 20, 30 & 40%), recombinant HGF, and anti-HGF and cell proliferation was measured by WST-1 assay. We further studied the protective role of AF on NEC in a rodent NEC model. Rat pups were delivered by cesarean section at 21.5 days of pregnancy and were exposed to hypothermia (40C for 10 minutes) and hypoxia (100% nitrogen for 60 seconds) every 12 hours to induce NEC. All rat pups (n=80) were divided into control (n=40, received only formula feed - rat milk substitute RMS) and experimental (n=40, received RMS + 30% rat AF). As the rat pups develop NEC, evidenced by distended abdomen or labored breathing, the pups were sacrificed by decapitation at any time of the experiment. All surviving pups were sacrificed at 96 hours and their small intestine was retrieved and studied for histopathology evidence of NEC (grade 0 to 4, 4 being the maximum). Results: Maximum cell proliferation was seen with 30% AF. HGF was the most abundant biological factor in the AF. IEC-6/RIE cell proliferation was significantly higher with recombinant HGF exposure as compared to no AF and this effect could be reversed by adding anti-HGF in the culture medium. The incidence (46 versus 65%; p<0.05) and severity (0.825 versus 1.625; p<0.05) of NEC was significantly lower in the experimental group as compared to the control group. Conclusion: HGF is the most abundant biological factor in AF and it increases intestinal cell proliferation which can be reversed by anti-HGF. AF reduces severity and incidence of NEC. Future studies will analyze the role of recombinant HGF in reducing NEC in the rodent model.
TOLL-LIKE RECEPTOR AGONISTS SYNERGIZE WITH CD40L/IFN. TO PROMOTE HUMAN DENDRITIC CELL SYNTHESIS OF IL-12
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Background: Dendritic cells (DC) are widely recognized as the most potent antigen-presenting cells for the induction of protective immunity against infectious pathogens and tumors. Maturation by CD40-CD40L interaction and IFN., allows DCs to provide critical signals for establishing memory CD8+ T cells via IL-12 production and upregulation of co-stimulatory molecules. Objective: To investigate additional signals that might synergize with CD40L and IFN., we sought to determine whether the addition of Toll-like receptor (TLR) agonists to CD40L and IFN. can increase IL-12 secretion as well as production of antigen-specific T cells. Methods: Human monocyte-derived immature dendritic cells (iDCs) established by standard 6-day culture in GmCSF/IL-4 were activated by CD40L/IFN. and optimal concentrations of TLR agonists. Supernatants were harvested and IL-12 production was assayed using ELISA for IL-12p70. IL-12 production in the presence of TLR agonists was compared to the baseline of CD40L and IFN. alone. For CD8+ T cell assay, activated DCs were harvested and pulsed with FluM1 peptide. Peptide-pulsed DCs were irradiated and incubated with purified CD8 T cells in the presence of low levels of IL-2. FluM1 tetramers were analyzed on day 10. Results: TLR agonists, 1, 4, 5, 6, and 8 resulted in significant increases in IL-12 production across donors as compared to CD40L and IFN. alone with mean fold-increases of 2.3, 4.0, 2.1, 3.5, and 8.8 respectively. TLR agonists 3, 7, and 9 did not have an effect on IL-12 production. TLR8 agonist in combination with TLR4 agonist resulted in an additional 25% increase in IL-12 production. Further evidence of synergy was supported by the capacity of FluM1 peptide-pulsed mDCs to stimulate antigen-specific CD8+ T cells in normal Flu sero-positive donors. The antigen-specific CD8 response, as assessed by tetramer-fold increase was significantly higher on day 10 using CD40L/IFN./TLR activated mDCs as compared to the conventional CD40L/IFN. activated mDC, with up to a four-fold increase using combined TLR agonists 4 and 8. Conclusion: TLR4 and TLR8 appear to be optimal agonists that promote IL-12 secretion by human monocyte-derived dendritic cells in the presence of CD40L and IFN. Our CD8 T cell stimulation shows that the increased IL-12 secretion translates to an increase in antigen-specific T-cell response. We conclude that multiple maturation signals are required to license DCs for the optimal generation of T cell memory.

HOST RESPONSES AND VIROLOGIC PROFILES IN PATIENTS WITH ACUTE LIVER FAILURE SECONDARY TO ACUTE HEPATITIS B VIRUS (HBV) INFECTION OR ACUTE EXACERBATION OF CHRONIC HBV
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Background: Acute liver failure (ALF) is often fatal but rare. HBV-related ALF occurs in a subset of infected patients and may be subdivided into HBV-ALF (if truly acute) or acute exacerbation on a background of chronic HBV (HBV-AOC). HBV-ALF and HBV-AOC may involve different host immune response mechanisms. Aims: We compared HBV-ALF and HBV-AOC in regard to host factors, admission viral loads (VL), viral clearance over 4 days and anti-HBc IgM, pre-core and core promoter mutations, and genotypes to confirm this suspicion. Methods: HBV-ALF was defined by patient history of recent HBV infection, without liver fibrosis and an always positive (pos) IgM anti-HBc. HBV-AOC was defined by having prior HBV infection and liver fibrosis. During 1998-2008, the ALF Study Group, a multi-center registry, enrolled 96 HBV patients (71 HBV-ALFs, 25 HBV-AOCs); admission sera were available on 56 HBV-ALFs and 20 HBV-AOCs; 20 HBV-ALFs and 6 HBV-AOCs had serial samples at 0, 2 and 4 days, but before transplant. VL and IgM were measured by real time PCR and ADVIA® Centaur, Anti-HBc IgM assay, respectively. Results: Admission VLs of HBV-ALF [median: 3.9; range (0-7.93) log10 IU/mL] were lower than HBV-AOC [6.37 (0-8.70)], P=0.015. VLs declined significantly in HBV-ALF (P=0.004) but not in HBV-AOC (P=0.51). HBV-ALF was associated with older age [median: 53; range (36-71) yrs] than HBV-ALF [40 (17-69)], P<0.001. HBV-ALFs had higher admission IgM anti-HBc titers [median: 87; range (4.49-1120) index value (signal/noise)] than HBV-AOCs [1.17 (0-1070)], P<0.0001. Asians accounted for 48% of HBV-AOC vs. only 7% of HBV-ALF [45% and 26%, P=0.001]. Genotype B comprised 52% of HBV-AOC’s vs. 10% of HBV-ALF that had mainly genotypes A (55%) and D (26%), P=0.001. HBV-AOC had more pre-core mutations (P=0.003) and HBsAg positivity (P=0.03) than HBV-ALF. HBV-ALF had higher overall survival (68%) than HBV-AOC (44%), P=0.03. Admission HBeAg, core promoter mutation, coma grade, and liver function markers did not differ between the two groups. Conclusions: Lower admission VLs, higher IgM anti-HBc titers, significant viral clearance, and sometimes-negative HBsAg (16%) on admission in HBV-ALF suggest that HBV-ALF exhibits a stronger host immune response than is seen in HBV-AOC. HBV-AOC had more Asian, genotype B, precore mutation, older age, and uniform presence of HBsAg. Distinguishing HBV-ALF from HBV-AOC may have pathogenetic and/or prognostic value.
INTERNALIZATION MECHANISMS OF BACILLUS ANTHRACIS SPORES BY HOST EPITHELIAL CELLS

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We recently reported that spores of Bacillus anthracis were internalized by a variety of non-phagocytic cells, including epithelial cells of the lung; that spores were capable of crossing a barrier of lung epithelial cells from the apical to the basolateral side most likely via a transcellular route; and that spores were found inside mouse lung epithelial cells in vivo (Russell et al., Cell Micro, 2007; Russell et al., Cell Micro, 2008; Russell et al., Infect Immun, 2008). These findings provide strong indication that B. anthracis spore uptake by host lung epithelial cells is an important aspect of its pathogenesis. Here we undertake studies to investigate the mechanisms underlying spore internalization by epithelial cells. Using a combination of gentamicin protection assays and fluorescence microscopy, we found that cytochalasin D, an actin polymerization inhibitor almost completely blocked spore internalization by epithelial cells (A549, HeLa and hSAECs). Actin filaments were enriched at the spore entry sites. Spore internalization was also reduced by the expression of dominant negative Cdc42 whereas expression of dominant negative RhoA and Rac1 did not have any inhibitory effect. Furthermore, a significant decrease of spore internalization was observed when phosphatidylinositol 3-kinase (PI3K) function was inhibited, either by inhibitors, wortmannin and LY294002, or by expression of a PI3K dominant negative construct (.p85a). PI3K was recruited and activated upon spore internalization, as demonstrated by the enrichment of Akt-PH-GFP, a probe for PI3K activation, around the spore invasion sites. In addition, PP2, a specific Src family tyrosine kinase (SFK) inhibitor, decreased spore internalization by epithelial cells significantly while its negative control compound PP3 did not have any effect. Finally, both PP2 and PI3K inhibitors decreased F-actin and Akt-PH-GFP enrichment while cytochalasin D only decreased the enrichment of F-actin. Overall, these results indicate that spore internalization by epithelial cells requires the polymerization and reorganization of F-actin mediated by Cdc42, and the activities of PI3K and SFK; and most likely, PI3K functions downstream of SFK but upstream of F-actin.

VLA-1 DEPENDENT ACCUMULATION OF A POPULATION OF EFFECTOR MEMORY CD4+ T CELLS TO THE LUNG FOLLOWING INFLUENZA INFECTION

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Background: During the immune response to influenza infection, activated T cells are distributed to both lymphoid and extralymphoid tissues. In contrast to lymphoid tissues, the majority of T cells in extralymphoid tissues have a highly activated phenotype. Although it is well established that extralymphoid tissues are enriched for effector T cells, little is known about how effector cells, particularly CD4+ T cells, are able to preferentially accumulate in sites such as the lung after infection. T cell persistence in extralymphoid sites may be related to expression of integrins that bind the extracellular matrix prevalent in these tissues. The alpha1beta1 integrin VLA-1 is the primary T cell binding partner for collagen IV, and is expressed on a population of CD4+ T cells after activation. Objective: We sought to determine the role of VLA-1 in the accumulation of effector CD4+ T cells to the bronchoalveolar lavage (BAL) following influenza infection. Methods: To study this, we developed a mouse model of infection with influenza A/WSN-OVAII, a recombinant virus with the OVA323-339 epitope inserted into the neuraminidase stalk. This enabled parallel monitoring of endogenous CD4+ cells and transgenic OVA-specific OT-II cells by ex vivo flow cytometry after infection. Results: During acute A/WSN-OVAII infection, VLA-1 is expressed on a minority of CD4+ cells. However, the proportion of VLA-1+ cells in the BAL specifically increases after viral clearance. VLA-1+ CD4 cells have a predominate effector phenotype and are capable of rapid effector cytokine response in the BAL within 24hr of a secondary influenza infection. Interestingly, VLA-1KO mice have a defect in their ability to accumulate effector CD4 T cells to the BAL but not lymphoid tissues following influenza infection, and VLA-1 deficiency on CD4 T cells alone is sufficient to observe this defect. VLA-1+ CD4 cells also express reduced markers of apoptosis in the BAL compared to VLA-1- cells, suggesting VLA-1+ CD4 cells may have an increased half-life in the lung. Conclusions: These data demonstrate that VLA-1 expression is integral in effector CD4+ cell accumulation to the BAL, and suggests effector T cells have specific mechanisms that enable their preferential localization to extralymphoid tissues. Future studies are aimed at evaluating the protective efficacy of vaccination strategies that elicit VLA-1+ T cells.
Crohns disease is a debilitating gastrointestinal disease affecting millions. Since it is mediated by the proinflammatory cytokines IL-12 and IL-23, the goal of this experiment was to develop a novel therapy utilizing a vaccine targeting the shared p40 subunit, thus resulting in a downregulation of those cytokines. Vaccines were developed by inserting a peptide from the p40 subunit into the hepatitis B core antigen (HBcAg). The highly immunogenic HBcAg's multimeric structure allowed a high epitope density per particle. By using three different peptides unique to the target subunit, three distinct vaccines were produced—C, D, and F. BALB/c mice were immunized three times at one week intervals with a vaccine, or with truncated HBcAg or saline as controls. Chronic colitis was induced in the animals using 2,4,6-trinitrobenzenesulphonic acid (TNBS) protocols. Mice were weighed one day after each injection. Throughout, sera were collected and levels of IL-12-specific IgG measured. In addition, the ability of this sera to inhibit the action of IL-12 was measured by quantifying the amount of IL-12-induced IFN-γ produced by spleen cells incubated with the sera. At week 13.5, mice were sacrificed and colon tissue collected. Inflammation was assessed semi-quantitatively using pathologist-scored H&E stained colon samples. The amount of collagen deposition was measured using Masson's trichrome stained colon specimens and a collagen assay. The total amount of IL-12p40 in each sample was quantified by ELISA. All vaccines induced serum IL-12-specific IgG. The IgG from vaccine C and F groups was found to inhibit the function of IL-12; vaccine D group showed no obvious inhibition. Vaccines C and F were found to decrease weight loss and recovery time post-injection, suppress intestinal inflammation, inhibit the fibrosis of chronic inflammation, and downregulate the production of p40 containing cytokines. It can be speculated that these vaccines halt the differentiation of naïve T cells into Th1 and Th17 cells, limiting the production of inflammatory cytokines and restoring the Th17/Treg balance. A concern is that cytokine levels may be severely reduced, thus impeding normal functioning. However, cytokine levels remain at a level still above that of normal. These induced antibodies target only those cytokines located in the extracellular compartment, and since normal cytokine processes occur in isolation at the immunological synapse, normal functioning is not affected.
CHRONIC HYDROCEPHALUS INDUCED ISCHEMIC CHANGES RELATING TO BLOOD VESSEL DENSITY AND VEGFR-2 IN CAUDATE NUCLEUS AFTER SHUNTING

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Background: Chronic hydrocephalus (CH) is characterized by increased cerebrospinal fluid (CSF) volume, with or without increased intracranial pressure (ICP), and has been treated by placement of a shunt to reduce CSF in the cerebral ventricles. While shunting can improve neurological symptoms the cause of these symptoms in hydrocephalus and the mechanism of shunt reversal remain unclear, especially in chronic (normal pressure) hydrocephalus. We have previously shown decreased blood flow, oxygen delivery and stimulation of Vascular Endothelial Growth Factor Receptor -2 (VEGFR-2) expression associated with angiogenesis in a model of chronic hydrocephalus. The goal of this study was to quantify changes in neuronal and glial VEGFR-2 expression and on blood vessel densities (BVd) in the caudate nucleus after shunting and to investigate their relationship. The caudate nucleus is a periventricular structure vulnerable to compression and or stretching during CH induced ventriculomegaly. Damage specifically to the caudate nucleus may be involved in gait impairment seen in chronic hydrocephalus. Methods: A total of fourteen (n=14) canines were part of this study and divided into three groups. CH-Shunted animals (CH-S, shunted at 12 weeks) (n=4) were compared with CH-Untreated animals (CH-U, =12 weeks) (n=5) and Surgical Controls (SC, =12 weeks), (n=5). The density of blood vessels and VEGFR-2+ neurons and glia was estimated using stereological cell counting methods. Values were expressed as a percent (%) density of VEGFR-2 + cells to the density of total cells in each region. Results: Chronic hydrocephalic animals had twice the amount of %VEGFR-2+ neurons compared to surgical controls. Shunted animals had a significantly lower %VEGFR-2+ neuronal expression (32%) compared to CH-U (50%) (p=0.01). However, BVd was highest in SC (1012 BV/ mm3) followed by CH-U (826 BV/ mm3) and was lowest in CH-S (675 BV/mm3) (p=0.05). Conclusions: In the caudate, shunting appears to partially reverse VEGFR-2 neuronal activation seen in chronic hydrocephalus but does not seem to have any effect on VEGFR-2 glial expression. The former is consistent with the hypothesis that hydrocephalus involves a chronic hypoxia which is resolved by CSF removal while the latter might suggest other factors may be involved in glial activation. The role of VEGF activation in chronic hydrocephalus may be evaluated further using agonists and antagonists and suggests a potential new mode of treatment.

EPILEPSY IN CHILDREN WITH ADHD

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BACKGROUND: Epilepsy and Attention Deficit/Hyperactivity Disorder (ADHD) are both common childhood disorders with a complex and poorly understood relationship. Prior studies have shown higher incidence of symptoms of ADHD in children with epilepsy, but few studies have examined epilepsy in children with ADHD. OBJECTIVE: To determine the incidence and the characteristics of epilepsy among a population-based birth cohort of children with ADHD. METHODS: We utilized a previously identified population-based birth cohort of 358 ADHD cases and 728 controls without ADHD. All medical records were reviewed from birth to age 20 for history of a seizure disorder. Seizure type, epilepsy disorder, dates and descriptions of seizures, predisposing causes of seizures, neurological examination, electroencephalography and brain imaging data, treatment, and family history of seizures were recorded. RESULTS: ADHD cases were 2.7 times more likely to have epilepsy than controls. ADHD cases with epilepsy developed seizures at an earlier age (median 5.5 years cases, 15 years controls), experienced more frequent seizures (more than monthly in 63% of cases, 17% of controls), and were less likely to respond to antiepileptic drugs (50% of cases failed an antiepileptic drug due to lack of efficacy, 17% of controls). Descriptive data on specific seizure types, neurological exam, treatment, and family history will also be presented. CONCLUSION: Our study suggests children with ADHD have a higher incidence of epilepsy than children without ADHD. In addition, epilepsy in children with co-morbid ADHD appears to be more severe than in those without ADHD. Clinical importance of this work includes heightened awareness of the increased incidence and severity of epilepsy among children with ADHD. Future studies with larger numbers and prospective study designs are needed to further examine this complex relationship between ADHD and epilepsy.
MATURATION OF ADULT GENERATED NEURONS IN THE DENTATE GYRUS OF AGING RHESUS MONKEYS
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Background: In the last decade, the generation of new neurons in the adult brain has become a well-accepted phenomenon. It has been documented in the dentate gyrus of rodents, monkeys, and humans. While many aspects of adult neurogenesis have been well-studied in the rodent brain, knowledge of neurogenesis in the primate brain is quite limited and the effect of aging on neurogenesis is unknown. One of the key questions is whether adult generated neurons actually become fully mature neurons, are incorporated into the brain, and survive long enough to contribute to neuronal function. Previous studies showed that the maturation process in young adult rhesus monkeys is slower than the 2 to 3 weeks demonstrated in rats, taking 3 to 4 months in the monkey to express neuronal phenotypes. In order to support memory processes, these neurons must survive for long periods but whether these adult generated neurons are actually present years later is unknown. Hypothesis: Adult generated neurons develop a mature phenotype, incorporate into the dentate gyrus, survive over a year as mature neurons and cognitive capacity depends on the number of such adult generated neurons. Methods: We investigated the survival of adult generated neurons in the primate brain by examining neurons labeled during division by a single injection of the thymidine analog, bromodeoxyuridine (BrdU). The subjects were seven rhesus monkeys ranging in age from 6 years (a young adult equivalent to an 18 year old human) to over 24 years of age (an elderly adult equivalent to a human over 72 years old). After post-BrdU injection survival times ranged from 7 months to 21 months (1.8 years), the brain tissues were harvested and examined using double label immunohistochemistry to identify BrdU positive cells that also expressed the neuron specific marker NeuN. The proportion of adult generated BrdU positive cells that expressed NeuN was confirmed using confocal microscopy. Results and Conclusions: Our preliminary data showed the presence of adult generated neurons in the dentate gyrus more than a year after they were generated. The data also suggest that generation and survival may decrease with age and hence might contribute to the mild age-related cognitive decline seen in normal aging. Future studies will include a larger sample size to confirm this and additional labeling with DoubleCortin (DCX) or Tuc-4, markers of immature neurons, to include the cells that are in the process of maturation.

NEUROPROTECTIN D1 MEDIATES CELL SURVIVAL IN AN IN VITRO MODEL OF PARKINSON’S DISEASE
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Parkinson's disease (PD) is a neurodegenerative disease caused by a loss of dopaminergic neurons mainly in the substantia nigra pars compacta. This project tested the hypothesis that neuroprotectin D1 (NPD1) attenuates dopaminergic neuronal death in a Parkinson's model using rotenone, MPTP, or MPP+. We used day-15 rat embryos and dissected out 1 mm3 of the ventricular mesencephalon for cell culture. 20,000 cells per well were plated in an 8-well chamber slide with B-27/N2 (Gibco) medium, and 2.5% serum. At 7 DIV, treatment was administered for 24 and 48 hours to induce cell death (100 nM rotenone, 100 µM MPTP or 100 µM MPP+). Also NPD1 (50 nM or 100 nM) was administered together with rotenone, MPP+, and MPTP. The preliminary results have shown that Rotenone (100 nM) induced cell apoptosis in up to 60% of the total cells. MPTP also induced cell apoptosis to some extent, whereas NPD1 rescued at least 50% of the cells, as revealed by TH, MAP1, and Hoechst staining. Pictures were taken with a deconvolution microscope at 10X and 20X enhancement. The preliminary data found that NPD1 (100 nM) rescued neurons from rotenone (50 nM and 100 nM) treatment and MPTP (100 µM) treatment. Rotenone (200 nM) in culture killed almost all of the cells. In conclusion, results show attenuation of dopaminergic neuronal death by NPD1 takes place in this cell culture model.
TARGETING AMYLOID OLIGOMERS FOR DIAGNOSIS AND TREATMENT FOR ALZHEIMER'S DISEASE
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Background: Alzheimer’s disease (AD) is one of the most devastating brain diseases. Nearly 5% of the population over 65 years old suffers from dementia. AD brains are invariably characterized by two pathological features: extracellular deposition of Aβ peptide, and intracellular accumulation tau protein, branded as amyloid plaques and neurofibrillary tangles (NFT) respectively. It has been reported that the extent of amyloid plaques and tangles accumulation does not correlate well with AD pathogenesis and that soluble Amyloid species correlate better with dementia, suggesting that oligomeric forms of both Aβ and tau may represent the primary toxic species in AD. Indeed, soluble prefibrillar oligomers have been implicated as primary causative agents in many different degenerative diseases. Objective: The key for developing an effective treatment for AD depends on better understanding of the complex aggregation pathways of both Aβ and Tau. In this study, we used a combination of sequence specific Aβ and Tau antibodies and novel conformation antibodies that we developed in our laboratory against different amyloid species, specifically anti-oligomers, anti-fibrils and anti-Tau oligomers to investigate the existence, location and conformation of each amyloid species in transgenic models, AD patient brain and CSF. Methods: After the production and characterization of the new conformational antibodies, we used these antibodies to analyze, characterize and classify the different amyloid species in AD brain samples and CSF, using Immunohistochemistry and biochemical techniques. Results: Our analysis of AD brains and age-matched controls demonstrate the presence of the toxic Aβ oligomers in AD brains at three different locations: intracellular, membrane associated and extracellular (in the vicinity of the non-toxic plaques). In addition, our results show for the first time the presence of Tau oligomers in AD brains, and elevated levels of these oligomers in CSF samples from AD patients. Conclusions: (A) Our studies suggest a dynamic changes of Aβ and Tau deposits in both location and conformation in addition to their role in the progression of AD. Similar analyses are being performed on samples from other neurodegenerative diseases. (B) Our results show for the first time that quantification of Tau oligomers in CSF using an anti-tau oligomer antibody is the best diagnostic tool reported to date for AD. Similar analysis will be performed on other biological fluid.

MATERNAL LOW PROTEIN DIET: DEVELOPMENTAL ORIGIN OF ADULT HYPERTENSION
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Background: Hypertension has become pandemic with an increasing number of individuals being afflicted each year. Epidemiologic studies in human and laboratory studies in Sheep, Guinea Pig and Rats indicate that malnutrition during gestation period can lead to fetal programming of adulthood hypertension in the offspring. Objectives: Studies have also established dys-regulation of the Renin Angiotensin System (RAS) as one of the major pathogenetic causes of hypertension. Moreover, epigenetic modifications of Adrenal Angiotensin Type 1 receptors (AT1) are known to occur with maternal low protein diet (MLPD) and may be responsible for developmental origins of hypertension. We hypothesized that maternal low protein, isocaloric diet during pregnancy programs the Brain Renin Angiotensin System in the fetus leading to adulthood hypertension.Methods: Pregnant mice were fed a normal protein diet (18%) or isocaloric MLPD (9% and 6%). Four mice dams from each group were sacrificed on 18 days of pregnancy to determine levels of brain mRNA and protein expression of Angiotensingen (AGT), Renin, Angiotensin Converting Enzyme (ACE) I, ACE II and AT1 & AT2 receptors. We used the non-invasive tail cuff system with novel volume pressure sensor recording (Kent Sci, Torrington, CT) to record BP. Data was analyzed using t-test and ANOVA, p<0.05 was considered significant. Summary of Results: Female protein deprived mice offspring show hypertension at 11 weeks of age, whereas males developed hypertension at 16 weeks of life. Maternal low protein diet caused low birth weight and rapid catch up growth. Our results indicate increased AGT and ACE1 but decreased AT2 expression of mRNA with MLP diet. Of interest, there was no change in the protein expression of AGT whereas decreased protein expression of ACE1 and AT2 receptors with MLP diet. There was no change in either mRNA or protein expression in brain renin, ACE2, AT1b or AT1b receptors. Conclusions: Our studies establish that maternal low protein diet programs hypertension in both males and female offspring. The programming of the renin-angiotensin system occurred in-utero; however, the functional manifestations such as increased BP are not observed until adulthood. The discrepancy between the mRNA levels and protein levels observed in the present studies may be the responsible for this delayed manifestation.
ANALYSIS OF SURVIVAL TRENDS IN PATIENTS WITH METASTATIC BREAST CANCER RECEIVING CHEMOTHERAPY: AN INSTITUTIONAL OVERVIEW

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Background: Since the approval of paclitaxel in 1994, a number of new chemotherapeutics with activity in metastatic breast cancer (MBC) have become available, yet limited data exist to support a trend towards improved survival with these agents. Objective: To determine whether newer cytotoxic chemotherapeutics have yielded improvements in overall survival (OS) for patients with MBC, using metastatic colorectal cancer (mCRC) as a comparison group. Methods: We undertook a retrospective chart review study of women with MBC diagnosed between 1985 and 2005 and compared OS for two consecutive time periods (1985-1994 and 1995-2005). We used survival data for patients with mCRC treated during the same time intervals as our comparison population. Female patients with MBC and patients with mCRC were identified from the City of Hope Cancer Registry. Tumor characteristics and receipt or non-receipt of chemotherapeutic agents were recorded. OS was calculated from the date of diagnosis of MBC or mCRC to the date of death or last follow-up. Results: A total of 385 patients with MBC receiving chemotherapy were identified with a median OS of 2.4 yrs in 199 cases diagnosed between 1985-1994 and 3.1 yrs in 159 cases diagnosed between 1995-2005 (HR 0.97, 95%CI 0.87-1.58; P=0.59). A trend towards improved survival in women with hormone receptor positive disease was observed; however, no difference in survival was observed between the two time intervals assessed. Specifically, median OS for patients with hormone receptor (ER) (+)/progesterone receptor (PR) (+) disease was 3.7 years during the first time period, as compared to 3.8 years during the second time period (HR 0.97, 95%CI 0.36-1.58; P=0.59). In contrast, median OS for patients with ER(-)/PR(-) disease was 1.9 years during the first period and 2.1 years during the second period (HR 1.05, 95%CI 0.57-1.93; P=0.87). In the comparison group, 638 patients with mCRC receiving chemotherapy were identified; median OS in 212 patients diagnosed from 1984-1995 and in 426 patients diagnosed from 1995-2005 was 1.2 yrs and 2.0 yrs, respectively (HR 1.69, 95%CI 1.33-195, P<0.0001). Conclusions: In mCRC, the addition of new agents has resulted in an improvement in OS. However, despite the addition of a number of new and effective chemotherapeutic agents, the OS for women with MBC has not improved.

EFFECT OF TARGETED INHIBITION OF mTOR COMPLEXES ON PROLIFERATION, APOPTOSIS AND CELL CYCLE PROGRESSION IN COLORECTAL CANCER

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Colorectal cancer (CRC) is the second leading cause of cancer death in the USA. The mammalian target of rapamycin (mTOR) acts downstream of PI3K to regulate cell growth, proliferation and survival. The mTOR kinase nucleates two distinct complexes, mTORC1 and mTORC2. The mTOR-RAPTOR complex (mTORC1) regulates translation initiation through the effectors S6K and 4E-BP1, while the mTOR-RICTOR-mSin1 complex (mTORC2) phosphorylates and activates Akt (Ser473), a key regulator of cell survival. Rapamycin inhibits the kinase activity of mTORC1; prolonged rapamycin treatment also inhibits mTORC2 assembly and Akt activation in certain cells. The purpose of the present study was to determine: (i) sensitivity of CRC cells to rapamycin treatment, and (ii) effect of targeting mTORC1 and mTORC2 upon CRC proliferation, apoptosis and cell cycle progression.

METHODS: HCT116, KM20, Caco-2 and SW480 human colon cancer cells were treated with rapamycin (20nM). Cells were also transfected with siRNA/shRNA directed against mTOR, RAPTOR or RICTOR. Effects on cell proliferation (Coulter counter cell counts), apoptosis (level of histone-associated DNA fragments) and cell cycle progression were analyzed. RESULTS: (i) Treatment with rapamycin significantly decreased the proliferation of HCT116 and KM20 cells (rapamycin sensitive); however, rapamycin did not alter SW480 or Caco-2 proliferation (rapamycin resistant). (ii) Immunohistochemical analysis showed that the mTOR complex components, RAPTOR, RICTOR and mSin1 are overexpressed in CRC tissue compared to adjacent normal tissue. In addition, expression of RICTOR was found to correlate with pAkt (Ser 473) expression in CRC tissues. (iii) Transient siRNA-mediated knockdown of RAPTOR decreased proliferation of KM20 cells (rapamycin-sensitive) only, while knockdown of RICTOR decreased proliferation of all four cell lines (both rapamycin-resistant and rapamycin-sensitive cells). (iv) Stable shRNA-mediated knockdown of mTORC1 and mTORC2 components leads to decreased proliferation, increased apoptosis and inhibition of G1-S phase cell cycle progression in HCT116 cells. CONCLUSIONS: The mTORC1 & mTORC2 components, RAPTOR, RICTOR and mSin1 are overexpressed in CRC. Transient inhibition of mTORC1, but not mTORC2, decreased the proliferation of SW480, Caco-2, KM20 and HCT116 cells. Thus, inhibition of mTORC2 activity represents a novel therapeutic strategy for treatment of rapamycin-sensitive and, more importantly, rapamycin-resistant CRCs.
THE UTILITY OF TISSUE DOPPLER IMAGING, CARDIAC BIOMARKERS, AND CARDIAC MRI IN PREDICTING EARLY LEFT VENTRICULAR DYSFUNCTION IN PATIENTS WITH HER-2 POSITIVE BREAST CANCER TREATED WITH HERCEPTIN

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BACKGROUND: Herceptin, a monoclonal antibody which targets the HER-2 receptor, reduces breast cancer mortality when used with anthracyclines in the adjuvant setting. The use of Herceptin, however, is limited by an elevated incidence of cardiotoxicity. Early indices of left ventricular (LV) dysfunction, using non-invasive cardiac imaging and/or biomarkers, would be useful for addressing the cardiac safety profile of Herceptin, thus avoiding the detrimental effects of heart failure. OBJECTIVE: To determine whether echocardiography with tissue Doppler imaging (TDI), cardiac biomarkers, and/or cardiac MRI (CMR) can demonstrate early subclinical LV dysfunction in patients with HER-2 positive breast cancer treated with Herceptin in the adjuvant setting. METHODOLOGY: A prospective study of 60 HER-2 positive breast cancer patients (2006-2008 inclusive) was performed, where patients were evaluated at 6 separate time points: i) pre-chemotherapy; ii) pre-Herceptin; iii) 3 months; iv) 6 months; v) 9 months; vi) 12 months after initiation of Herceptin treatment. At each time point, patients underwent echo with Tissue Doppler imaging, and biomarkers. CMR was performed at baseline and at 12 months. RESULTS: Out of the 60 patients evaluated, 12 (20%) developed Herceptin induced cardiotoxicity. In those affected, Tissue Doppler imaging indices decreased earlier than conventional LVEF measurements while cardiac biomarkers remained unchanged. CONCLUSION: Tissue Doppler imaging is a sensitive, non-invasive echocardiographic technique that can be used to detect subtle subclinical LV dysfunction in patients undergoing adjuvant Herceptin therapy prior to decrease in conventional LVEF. Cardiac biomarkers including troponin T, CRP, and BNP levels were not indicative of subtle LV dysfunction in this patient population. DE-CMR can be used to detect scarring of the lateral ventricular wall confirming Herceptin induced cardiotoxicity. Further studies are needed to determine whether positive delayed enhancement on CMR is temporary or permanent following discontinuation of Herceptin therapy.

APPLYING PROTEOMICS BASED MASS SPECTROMETRY IMAGE PROFILING TO PANCREATIC CANCER

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Background: Pancreatic cancer is the fourth leading cause of cancer death. Fewer than 5% of patients survive five years. Only about 20% are operative candidates, after which, the 5-year survival rate only approaches 25%. Mass spectrometry is an analytical tool that identifies chemical composition of a sample based on mass to charge ratio (m/z) and has been used to characterize and identify small molecules, proteins, and fatty acids. Few studies have used mass spectrometry to analyze the proteome of those with pancreatic cancer. There have been no publications to date illustrating the expressed use or utility of mass spectrometry based image profiling to identify protein changes within pancreatic cancer operative specimens. Objective: To apply histology directed matrix-assisted laser desorption/ionization (MALDI) mass spectrometry (MS) image profiling to pancreatic cancer specimens for the identification of specific protein changes present in malignant tissue. Methods: Ten human tissue samples were taken from operative specimens with and without pancreatic cancer. Tissues were frozen and cut into 12 micron sections, thawed onto a MALDI plate and fixed. Serial sections were taken for H and E histological guidance. Sinapinic acid matrix was then to applied to regions considered to be of pathological interest. MALDI-MS generated spectra were then acquired for each tissue sample. By applying various specialized software packages, spectra were processed and configured for comparison by standard statistical analysis. Results: Cancer specimens were found to express proteins of varied molecular weight, some of which have been identified in serum from corresponding analysis by our group in addition to other groups. Of interest included molecular weights that corresponded within a few Daltons to parent or isoforms of apo-lipoproteins (13812 m/z), serum amyloid A (1327 m/z), thioredoxin (13878 m/z), and defensins (3374/ 3446 m/z) to name a few. Conclusions: This is the first study in pancreatic cancer of it’s kind and it is outwardly apparent from this small pilot study the that direct MALDI-MS analysis of pancreatic cancer vs. benign tissues is worth pursuing further, and has yielded potentially interesting markers, some of which were previously found in serum. Therefore, it is expected that a larger more detailed study will yield more concrete answers with the potential for better non-invasive diagnostics in addition to potential drug targets.
F-5
PREOPERATIVE C-REACTIVE PROTEIN LEVELS PREDICT METASTASIS AND 1-YEAR MORTALITY IN PATIENTS RECEIVING POTENTIALLY CURATIVE NEPHRECTOMY FOR LOCALIZED RENAL CELL CARCINOMA

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Introduction: Recent studies have identified preoperative systemic inflammation, represented by elevated concentrations of C-reactive protein (CRP), as a predictor of 5- and 10-year mortality in renal cell carcinoma (RCC), independent of tumor stage and grade. However, the value of preoperative CRP in predicting metastasis and 1-year mortality has not been assessed. The aim of this study was to assess whether preoperative CRP levels predict likelihood of metastasis and 1-year mortality among patients undergoing potentially curative nephrectomy for localized RCC. Methods: 217 patients undergoing potentially curative resection for localized renal cell carcinoma were enrolled. CRP levels were measured one month prior to nephrectomy. Death was defined as disease-specific mortality. Patients with known nodal or metastatic disease were excluded. Results: The average patient age was 62 (range = 35 - 91). During the mean follow-up of 12 months, 41 patients developed metastases, predominantly to the bone, brain, lungs, and viscera, and 17 patients died. The average preoperative CRP value for patients who developed metastases was 64.76 mg/dL, while the average preoperative CRP value for patients who did not develop metastases was 19.50 mg/dL. After controlling for age, BMI, race, gender, tumor size, and grade, every 1 unit increase in preoperative CRP level increased the odds of metastasis by 1.023 (95% CI: 1.009, 1.036; p=0.001). The average preoperative CRP value for patients who died was 84.36 mg/dL, while the average preoperative CRP value for patients who did not develop metastases was 20.32 mg/dL. After controlling for age, BMI, race, gender, tumor size, and grade, every 1 unit increase in preoperative CRP level increased the odds of metastasis by 1.016 (95% CI: 1.004, 1.028; p=0.009). Conclusions: The current study is the first to suggest that preoperative C-reactive protein levels predict the likelihood of metastasis and 1-year mortality in patients undergoing potentially curative resection of localized RCC. Upon further verification, this clinical tool could help identify patients for novel adjuvant therapies and stricter post-operative screening of metastases.

F-6
UTILITY OF TISSUE DOPPLER AND STRAIN IMAGING IN THE EARLY DETECTION OF TRASTUZUMAB AND ANTHRACYCLINE MEDIATED CARDIOMYOPATHY

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Trastuzumab provides considerable therapeutic benefits in the adjuvant setting of breast cancer. Its use however is limited by an elevated incidence of cardiotoxicity when used in combination with doxorubicin. Although Myocet (liposomal-encapsulated doxorubicin) is less cardiotoxic, its cardiac safety profile with trastuzumab is not well known. The aim of this study was to determine if sensitive indices of left ventricular (LV) dysfunction, specifically tissue Doppler imaging using echocardiography, would be useful in addressing the early detection of trastuzumab and anthracycline-mediated cardiotoxicity. Wild-type C57Bl/6 mice (n=60) received one of the following drug regimens: (1) control, (2) doxorubicin, (3) Myocet, (4) trastuzumab, (5) doxorubicin and trastuzumab, or (6) Myocet plus trastuzumab. TDI-derived peak endocardial systolic velocity, strain rate, and LV ejection fraction were measured serially for 5 days. On day 5, the hearts, lungs, and livers were removed for histopathologic and Western blot analyses. Mice treated with Myocet plus trastuzumab demonstrated minimal cardiotoxicity compared with those treated with doxorubicin plus trastuzumab. Progressive LV dilatation and LV systolic dysfunction were observed by day 4 of treatment with doxorubicin plus trastuzumab, compared with preserved LV ejection fraction in the remaining groups. TDI parameters decreased within 24 hours in the doxorubicin alone and doxorubicin plus trastuzumab groups and predicted early mortality. Average liver wet to dry weight ratios were significantly elevated in mice treated with either doxorubicin or doxorubicin plus trastuzumab, indicating advanced heart failure. At the cellular level, the greatest amount of damage was seen in hearts of mice treated with doxorubicin plus trastuzumab. The amount of apoptosis was significantly lower when Myocet was combined with trastuzumab rather than doxorubicin. The survival rate was only 20% at day 5 in the doxorubicin plus trastuzumab group, whereas 100% of mice receiving Myocet plus trastuzumab survived the 5 days. Thus, TDI can detect early LV dysfunction prior to alterations in conventional echocardiographic indices and predict early mortality in mice receiving doxorubicin and trastuzumab. Also, Myocet and trastuzumab was shown to be a safer combination than doxorubicin and trastuzumab in an acute murine model of chemotherapy-induced cardiotoxicity.
Mantle cell lymphoma (MCL) is an aggressive non-Hodgkins B-cell lymphoma with median patient survival of only three to four years. MCL is characterized by a t(11;14)(q13;q32) translocation causing overexpression of cyclinD1, a cell cycle regulator. Current treatments include combinative chemotherapies, radiation, and small molecule inhibitors. While these treatments lower tumor burden, new treatments are needed to target therapy-resistant cells responsible for relapse in patients. Recently, NOD-SCID mice were inoculated with Granta-519 MCL then treated with cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP). Following relapse, tumor cells were isolated from kidneys and livers of mice and therapy-resistant MCL cell lines were established. Preliminary studies demonstrated that, besides having resistance to CHOP, these cells display unique gene expression patterns based on microarray expression data and exhibit amplified proliferative properties in vitro and in vivo. Also, these cells portray higher frequencies of side-population cells based on flow cytometric analysis after Hoechst 33342 staining, indicating stem-like properties. Additionally, the therapy-resistant cells exhibit altered expression of hedgehog signaling molecules compared to parental MCL, which is interesting due to recent elucidation of the role of hedgehog signaling in the proliferation and therapy-resistance of MCL (Hegde, et al. Mol Cancer Ther 2008; 7[6]:1450-60). Therefore, to eliminate therapy-resistant cells in vivo, novel chemo-immunotherapeutic drug regimens were devised to target hedgehog signaling in relapsing cells. Specifically, NOD-SCID mice were inoculated with MCL then treated with CHOP therapy to lower bulk tumor burden. Mice were then treated with antisense oligonucleotides to GLI transcription factors --mediators and targets of hedgehog signaling, or cur691 --inhibitor of hedgehog signaling (Genentech Corporation). Each of these treatments was given separately, or combined with MCL-specific adoptive T cell therapy (ATT). Mice given these treatments combined with ATT showed significantly increased survival over mice given CHOP treatment alone. Taken together, these results demonstrate the value of using combined chemo- and immunotherapeutic strategies to specifically target therapy-resistant relapsing tumor cells and offer evidence for clinical efficacy in providing long-term tumor-free survival in patients with MCL.
**Poster 1**

**INDUCED BRUGADA TYPE ECG, A SIGN FOR IMMINENT MALIGNANT ARRHYTHMIAS**

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Background: The Brugada syndrome is a clinical-electrocardiographic diagnosis based on the occurrence of syncopal or sudden cardiac death (SCD) episodes in patients without structural heart disease and a characteristic ECG pattern of right bundle branch block and ST segment elevation in leads V1 to V3. Approximately, 20% of Brugada Syndrome patients are carriers of genetic mutations that cause sodium channelopathies. However, the typical electrocardiographic pattern can also be seen acutely associated with other disease and disease states. The implications of presenting with this pattern have not been assessed. Objectives: The purposes of this study are the following: (1) to demonstrate the significance for early detection of the Brugada type ECG in a medical emergency; (2) to determine the risk of cardiac arrhythmias and sudden death in patients who present with a Brugada type ECG during acute medical situations; (3) to assess the role of genetics in the development of malignant arrhythmias and SCD in acutely ill patients presenting with the typical Brugada pattern on their ECG.

Methods: The study population consisted of 47 cases of patients with an acute presentation of Brugada type ECG (69% male, mean age 48 16.2 years). Clinical characteristics, genetics and outcome of the individuals have been investigated. Results: The ECG was developed during a febrile episode in 16 patients, due to a medication (cocaine, anesthetics, antiarrhythmics, antidepressants) in 26 and due to electrolyte abnormalities in 5 patients. Fifteen patients developed sudden cardiac death (SCD) during the event, of whom six the SCD was associated with fever and six with propofol. Additionally, three patients had syncope, two had documented VT episodes and eight had atrial fibrillation. Genetic analysis was performed in 26 individuals, and 4 had a mutation in SCN5A.

Conclusion: The development of Brugada type ECG during an acute process is a medical emergency. In our series, 51% of the patients had events including 38% who developed cardiac arrest. The rapid identification of the Brugada type ECG in acute situations is crucial to prevent fatal consequences, regardless of the genetic status of the patients. Genetic carriers of a sodium channelopathy should be aware that some medications and disease states may increase their risk of arrhythmias. In our study, 75% of SCN5A mutation’s carriers developed malignant arrhythmias.

**Poster 2**

**PITX2: LINKING ATRIAL FIBRILLATION AND LEFT-RIGHT ASYMMETRY**

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Background: Atrial fibrillation (AF), the most common adult arrhythmia, is generally regarded as an acquired disorder, but recent familial AF studies indicate that it is genetically linked. However, AF pathogenesis is poorly understood. Recent human genetic studies identified variants adjacent to the Pitx2 locus associated with risk of AF, making Pitx2 a candidate AF regulatory gene. The homeobox transcription factor Pitx2 encodes 3 isoforms and Pitx2c performs a critical role in left-right asymmetry (LRA) of heart. LRA is recognized as a causative factor in syndromic congenital heart disease, but has not been given high priority by clinicians. Objective: In this study, we investigate whether Pitx2 plays an important role in the developing heart to dissect the pathogenesis of AF. We hypothesize that Pitx2 directly represses genes required for right-sided atrial characteristics in the left atrium, such as Tbx3 and Shox2.

Methods: Conventional 6 lead surface ECG and 4 lead bipolar intracardiac electrograms were recorded simultaneously in wild type and Pitx2 heterozygous (Pitx2null+/-) mice. Other approaches used in this study include bioinformatics assay, whole mount lac Z staining, whole mount in situ hybridization, quantitative real time RT-PCR, chromatin immunoprecipitation (ChiP) and luciferase assay. Results: Normal electrical impulses originate in the sinoatrial node, which is a right-sided cardiac structure that requires Tbx3 and Shox2 for its development. Our data indicate that Pitx2null+/- adult mice exhibit AF possibly due to disorganized electrical impulses originating from the left atrium. Moreover, our data reveals expansion of Tbx3 and Shox2 in Pitxnull/- mutant embryos. Notably, we identified conserved Pitx2 binding sites in Tbx3 and Shox2. Taken together, our data suggest that Pitx2 has critical role in AF pathogenesis and directly represses Tbx3 and Shox2.

Conclusions: This study reveals for the first time, a role of Pitx2 in AF pathogenesis and links transcriptional regulation, LRA and AF. This will hopefully give us a better understanding of the fundamental mechanisms of AF pathogenesis to facilitate new approaches to the diagnosis, prevention and treatment of AF.
Poster 3

AORTIC SINUS WALL DIMENSIONS AND GEOMETRY IN FRESH AUTOPSY SPECIMENS
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Background: The native aortic root has a complex three dimensional geometry with three bulging sinuses. The various root replacement surgical methods require detailed knowledge of sinus anatomy and variability. Though the literature gives much information regarding many aortic root dimensions there is no data on sinus wall true tissue dimensions and how much sinus walls contribute to the outward ballooning. Objective: To obtain macroscopic tissue dimensions and geometry of Valsalva sinuses in normal anatomical specimens. Methods: In fresh autopsy specimens with no aortic valve pathology (n=30) the aortic root was dissected away from the heart. After measuring inflow and outflow diameters the root was opened longitudinally at the commissural line between the right coronary and non-coronary sinuses. All three sinuses were separated from the aortic annulus, their outward curvature was flattened with small radial incisions inferiorly and the tissue dimensions: length, width and intercommissural distance were measured. Various relational patterns within the aortic root were determined from these data. Results: The overall aortic root geometry was slightly cone-shaped in younger individuals and tended to take a reverse cone shape in specimens from older subjects. Within one aortic root the three sinus wall's dimensions were typically asymmetrical and tended to have a flat oval (and not tear-drop) shape. In 60% of the cases the sinus wall significantly widened 6-12mm below the sinus ridge thus contributing to the outward ballooning. On the three dimensional geometry there were still visible sinus bulges when the sinus wall tissue did not widen (32%) or even when it narrowed (8%). The sinus walls within a single aortic root had a widening pattern in 24 of the 30 specimens. There were no aortic roots with completely symmetrical sinus dimensions in our series. Conclusions: Our measurements of fresh autopsy specimens confirm that the aortic root invariably contains three different size sinuses. The bulging patterns of the three sinuses were not universal within a particular root, but an outward bulge was present even without excess tissue within the sinus wall. This suggests that the subcommissural triangles wedged between the sinuses are also important determinants of the ultimate sinus curvatures. These data further complicate the three dimensional asymmetry of the native aortic root that has to be rebuilt in valve sparing root replacement surgery.

Poster 4

THE NORMAL AND ABNORMAL OWL MONKEY (AOTUS SP.) HEART: LOOKING AT CARDIOMYOPATHY CHANGES WITH ECHOCARDIOGRAPHY AND ELECTROCARDIOGRAPHY
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Cardiovascular disease, especially cardiomyopathy, is the major cause of death among owl monkeys (Aotus sp.) at the Center for Neotropical Primate Research and Resources. The purpose of this study was to use echocardiography and electrocardiography to establish normal values for aged owl monkeys and identify parameters to recognize cardiomyopathy in owl monkeys. Forty-eight owl monkeys were studied; forty were ten years or older (aged) and ten were five years old (young). Eight aged owl monkeys were identified with cardiomyopathy. There were no differences in the electrocardiogram parameters between the groups. The left ventricular posterior wall thickness increased by 23% for the aged and 28% for the cardiomyopathy when compared to the young group and was identified as a age related increase in owl monkeys. In the cardiomyopathy group, ejection fraction and chamber size were decreased by 40%, while left ventricular diameter at diastole and systole was increased by 19% and 36%, respectively, when compared to the aged group. Left ventricular diameter, chamber size, and ejection fraction are identifying measurements for cardiomyopathy in owl monkeys. Studies using non-human primates may have increased variability because some animals may be wild caught or their genetic backgrounds may not be well-characterized. In addition, there was a small sample size for the young group. The owl monkeys studied exhibited the stages of heart failure recognized in humans. The study of cardiomyopathy in owl monkeys is not only important in maintaining a self-sustaining colony, but it is also a promising model for human cardiovascular disease.
HYPOTHERMIA AFTER ACUTE ISCHEMIC STROKE: IS LESS MORE?

Background: A growing number of cities around the world now follow international guidelines calling for the immediate use of mild hypothermia (32-35°C) for 12-24 hrs after cardiac arrest. While the evidence for hypothermia after cardiac arrest is strong, trial outcomes of hypothermia after acute ischemic stroke have been disappointing. Objective: We analyzed existing clinical trials both to evaluate how hypothermia has been applied after acute stroke, and to identify variables associated with mortality. Methods: PubMed was queried using the terms “hypothermia”, “stroke”, and “human”. We excluded studies where hypothermia was not administered after acute ischemic stroke, retrospective reports, and those studies that did not report patient mortality. From the resulting studies, we extracted data relating to study design, patient characteristics, cooling methodology, and patient mortality. Summary statistics, weighted for the number of subjects cooled, were calculated. The aggregate mortality rates of control patients and patients receiving hypothermia were calculated. Linear regression was performed on mortality rate for patient characteristics and cooling parameters. The level of statistical significance was set at 0.05. Results: Ten unique studies reported the mortality rate of patients receiving hypothermia following acute ischemic stroke. All were prospective cohorts of seven patients or more; five had control groups. In total, 181 patients received hypothermia. The average time from symptom onset to the initiation of cooling was 15.5 [8.2] hours (average [SD]). Hypothermia was applied at an average rate of 0.8 [0.8] °C/hour, to an average target temperature of 33.8 [1.3] °C, for an average duration of 74.5 [111.6] hours. Among all patients who received hypothermia, the mortality rate was 26.5% (95% CI 6.4%). In the five trials with control groups, the mortality rate among those receiving hypothermia differed significantly from that of the control group (25.0% vs 13.7%; p = 0.046). In linear regression, only target temperature was significantly associated with the study mortality among those receiving hypothermia (-9.5% mortality/°C, p for slope < 0.0001). Conclusions: Thus far, clinical trials of hypothermia after stroke have typically administered mild hypothermia for more than 24 hours at more than three hours after the onset of symptoms, with little benefit. Future stroke trials may benefit from a re-examination of cooling parameters used to date.

ASCENDING AORTIC ANEURYSM IN A HIV+ PATIENT

Background: We present a case of a 46 year old male who has a history of human immunodeficiency virus (HIV) who was found to have an 8.0 cm x 7.6 cm ascending aortic aneurysm. The patient has no family history or physical exam findings suggestive of a connective tissue disorder. Given his young age, the possibility of HIV as a contributing factor to aneurysm formation was further evaluated. Objective: To compare the histopathology report of the excised aortic aneurysm tissue to the findings and proposed mechanisms previously reported in the limited available literature. Methods: The excised tissue specimen was prepared in conventional form using hematoxylin and eosin and elastic von Gieson stains. A literature search was then conducted using the keywords human immunodeficiency virus, vasculitis, and aneurysm. The results were analyzed for relevance, and the references of selected papers were reviewed as additional sources of information. Results: The histopathology revealed mild fibrosis of the adventitia and patchy areas of mild to moderate chronic mononuclear inflammation of the vasa vasora. The media showed varying degrees of fibrosis, loss of smooth muscle, fragmentation of elastic fibers, and sparse chronic inflammation. The intima was mostly spared with fragmentation and duplication of the internal elastic lamina being the noted features. The literature review returned four possible mechanisms: endothelial cell dysfunction, smooth muscle cell infection, vasculitis of the vasa vasorum, and drug related lipodystrophy syndrome. Conclusions: Although HIV infection is primarily thought of affecting the immune system, it is clear that every organ system is subject to the effects of the virus. Even though a direct causative mechanism cannot be definitively established based on our findings, the evidence presented reveals how HIV infection can cause cellular dysfunction and aneurysm formation.
Poster 7
INHIBITION OF XANTHINE OXIDASE IMPROVES LEFT VENTRICULAR DIASTOLIC FUNCTION AND MITOCHONDRIAL FUNCTION IN ACUTE VOLUME OVERLOAD IN THE RAT HEART
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Background: Volume overload (VO) heart failure is marked by progressive left ventricular (LV) dilation and dysfunction driven by an increase in LV diastolic wall stress. Mechanisms underlying the myocardial response to VO are poorly understood and no medical therapy exists. Xanthine oxidase (XO) is characterized as a major cause of oxidative stress in the myocardium in various forms of heart failure. Our laboratory has found XO to be increased in LV biopsies from patients with chronic isolated mitral regurgitation taken at the time of reparative surgery. However, whether XO-induced oxidative stress plays a role in LV function following VO is unclear. To establish this relationship we inhibited XO in an established model of VO, the aortocaval fistula rat (ACF).

Objective: Determine if XO inhibition in the volume overloaded rat heart improves LV diastolic function and wall stress.

Methods: Age-weight matched Sprague-Dawley rats were randomly assigned to either ACF or sham surgery. Allopurinol (100 mg/kg) was administered at time of surgery by gastric gavage. Standard tissue collection, combined echocardiography/high-fidelity pressure analysis, and mitochondrial respiratory studies were performed at 1 day. All data are presented as mean ± standard error. Statistical analysis was performed using 2-way anova with Student-Newman-Keuls post-hoc test. Results: XO activity in LV tissue was increased in ACF vs sham operated rats (921 ± 49 vs 690 ± 71 µU/mg). LV end diastolic pressure (LVEDP) was increased in ACF vs sham (7.6 ± 0.6 vs 2.6 ± 0.7 mmHg p<0.001). XO inhibition normalized LVDEP in the ACF as compared to Sham (4.3 ± 0.6 vs 3.8 ± 0.8 mmHg). LV end diastolic wall stress was increased in ACF vs sham (7.9 ± 0.9 vs 2.4 ± 0.9 g/cm²) and was improved following XO inhibition (ACF 7.9 ± 0.9 vs ACF+Allopurinol 5.1 ± 0.9 g/cm² p=0.04). In isolated cardiac mitochondria, sensitive targets of oxidative stress, ADP-induced mitochondrial oxygen consumption (state 3) was significantly impaired in ACF vs sham rats and was normalized with allopurinol treatment. Conclusions: ACF rats, as in patients with VO, display an increase in LV XO activity. Inhibition of XO improves LV diastolic function and wall stress at 1 day of ACF. Isolated LV mitochondria display depressed reserve function in the ACF heart which is normalized with allopurinol treatment. These results implicate XO-derived oxidative stress as the cause of diastolic and mitochondrial dysfunction.

Poster 8
ATYPICAL MYCOSIS FUNGOIDES PRESENTATION IN CHILD
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Mycosis fungoides (MF) is a dermatologic condition characterized by the accumulation of malignant T cells within the skin. Clinically this presents as either erythematous patches, plaques, or tumors, often in conjunction with scales. Overall, MF is an extremely rare syndrome comprising less than 7 cases per million people in the United States. It is exceedingly unusual for MF to present in the pediatric population; less than a total of 50 cases have been described in the literature and one extensive retrospective study concluded that only 4% of MF cases arose before age 16. MF has many distinctly different features when presenting in children as compared with adults including the probability of hypopigmentation, poikiloderma, and underlying malignant T cell type. In the course of this presentation we will discuss the case of a 12 year old black female with biopsy proven stage I MF, symptomatic since the age of 8. Her case incorporates a rare presentation of papulosquamous MF involvement in her hands and feet as well as hypopigmented patches on her chest. In addition, we will discuss the intricacies of this exceedingly rare case, including the primary diagnostic approach and multiple modes of treatment utilized, as well as provide gross and microscopic pathology and radiologic correlation.
Poster 9
MATRIX METALLOPROTEINASE EXPRESSION IN NEPHROGENIC SYSTEMIC FIBROSIS
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Background: Nephrogenic systemic fibrosis (NSF) is a devastating fibrosing disease recently recognized. Affecting a subset of patients with renal insufficiency, it has a strong association with exposure to gadolinium(Gd)-based contrast agents used in magnetic resonance imaging. The resulting thickened, hardened skin can become physically disabling. Gd has been visualized in patients' skin biopsies. However, the mechanism of fibrosis has yet to be elucidated. The balance between matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinase (TIMP) play a role in normal and abnormal wound healing of the skin. Objective: We seek to investigate the presence and/or amount of MMPs and TIMP in skin biopsies of patients affected by NSF, thereby learning more about the underlying fibrosis mechanism. Methods: To investigate the role of MMPs in NSF, we utilized immunohistochemistry to visualize MMP-1, MMP-2, MMP-9 and TIMP-1 expressed in fibrocytes in sixteen biopsies from eight NSF patients. Results were read using a semiquantitative scale with - (no staining), + (<25%), ++ (25-50%), +++ (50-75%), and ++++(>75-100%). Results: TIMP-1 was markedly elevated in all biopsies; regardless of time elapsed since symptom onset. This inhibitor of MMPs reduces the breakdown of collagen, resulting in fibrosis. MMP-1, which cleaves type I collagen, was absent or sparse. MMP-2 and -9, which degrade type IV collagen, were increased in varying amounts compared to normal skin. In normal wound healing, these regulators eventually return to normal levels. Conclusion: Our findings suggest the fibrosis in NSF is unregulated or that the insult itself (Gd) is constantly re-injuring the skin and reactivating fibrosis.

Poster 10
DERMAL MUCINOSIS AS A SIGN OF VENOUS INSUFFICIENCY
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Background: Cutaneous mucinoses are characterized by abnormal deposition of dermal mucin, an amorphous substance composed primarily of hyaluronic acid and sulfated glycosaminoglycans. Dermal mucinoses are classified as primary, in which mucin deposition is the main histologic feature, or secondary, in which mucin is a secondary finding as in dermatomyositis or lupus erythematosus. Objective: We present two cases of dermal mucinosis secondary to venous insufficiency, and propose a pathogenic mechanism. Methods: Two cases are presented. Patient one presents with a 9-year history of a painful, edematous 3x8cm lower extremity plaque and patient two with a 5-year history of a tender, violaceous 8x5cm lower extremity plaque. Both patients have a history of chronic venous insufficiency. Biopsy was performed for histopathology. Results: Patient 1: Biopsy demonstrates abundant dermal mucin deposition with increase in blood vessel density in the dermis. Patient 2: Biopsy demonstrates striking mucin deposition in the upper and mid-dermis. Vessels and scattered vascular spaces are present within collections of mucin. Both patients have a history of chronic venous insufficiency. Biopsy was performed for histopathology. Results: Patient 1: Biopsy demonstrates abundant dermal mucin deposition with increase in blood vessel density in the dermis. Patient 2: Biopsy demonstrates striking mucin deposition in the upper and mid-dermis. Vessels and scattered vascular spaces are present within collections of mucin. Both patients were diagnosed with dermal mucinosis in the setting of chronic venous insufficiency. There is no evidence to support a primary cutaneous mucinosis. Scleromyxedema is associated with a monoclonal paraproteinemia which neither patient shows on protein electrophoresis. Neither patient demonstrates laboratory or clinical findings consistent with collagen vascular disease or other secondary mucinosis such as thyroid dysfunction, lupus erythematosus, dermatomyositis, scleroderma, granuloma annulare, graft-versus-host disease, or mucin deposition post-UV or PUVA treatment. Hypoxia may play a central role in the pathogenesis. Venous insufficiency is known to decrease local tissue oxygenation. Chondrocytes increase hyaluronate production due to reduced oxygen tension; local hypoxia could similarly increase fibroblast hyaluronate synthesis in the dermis. Hyaluronic acid, known to stimulate angiogenesis, may explain the increased vascularity of both specimens. Hyaluronic acid addition to bovine endothelial cells and hyaluronan-based grafts implanted in porcine arteries have been shown to act as microvascular scaffolds for angiogenesis. Conclusions: We demonstrate a new entity of secondary dermal mucinosis due to chronic venous insufficiency, in which tissue hypoxia is postulated to cause increased mucin production and possible vascular proliferation.
Poster 11
INCREASED LEVELS OF CD4+25high REGULATORY T CELLS IN PATIENTS WITH CUTANEOUS T-CELL LYMPHOMA AFTER EXTRACORPOREAL PHOTOPHERESIS
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Extracorporeal photopheresis (ECP), a systemic treatment involving the reinfusion of UVA-psoralen treated lymphocytes, is used effectively to treat Sézary Syndrome (SS), the leukemic variant of cutaneous T-cell lymphoma (CTCL). ECP is thought to control SS in part through direct induction of lymphocyte apoptosis, but its effects on the immune system beyond apoptosis remain uncharacterized. In a prospective trial, we have studied 5 SS patients undergoing ECP treatment and correlated the clinical response by skin-weighted assessment tool (SWAT) with the induction of regulatory T cells (T-reg). Freshly isolated peripheral blood mononuclear cells (PBMCs) were evaluated for the levels of CD4+CD25high T cells by flow cytometry at baseline and post-ECP on Day 2, 1 month, 3 months, and 6 months. Total RNA extracted from PBMCs was used to measure CD25 (IL-2Ra) and Foxp3 mRNA by QT-RT-PCR. The numbers of CD4+CD25high T cells, and the expressions of CD25 and Foxp3 mRNA varied among patients at baseline. Compared to baseline, at 6 months post-ECP, 5 of 5 patients had increased percentages and absolute numbers of CD4+CD25 high T cells. The highest increase was found in the clinical responder, Pt#2, from 0.31% to 27.3%. Compared to baseline, the expression of CD25 and Foxp3 mRNA also increased at 6 months post-ECP in 3 of 4 examined CTCL patients (Pt#1, #2 and #4). Continuous rising levels of both CD25 and Foxp3 mRNA were seen in responders, Pt#1 and Pt#2, during the treatment course. The highest levels were detected at 6 months post-ECP with 8.4- and 9.8-fold increase in CD25 expression, and 13.1- and 17.4-fold increase in Foxp3 expression, respectively. These two patients experienced partial clinical responses and decreased circulating tumor cells with ECP. These results indicate that CD4+CD25 high Tregs are induced in some of the CTCL patients by ECP, and could suppress the malignant clone leading to disease improvement. Ongoing studies with more patients will help support our results.

Poster 12
TAZAROTENE'S CHEMOPREVENTION EFFICACY ON PRECLINICAL MODELS OF MEDULLOBLASTOMA AND BASAL CELL CARCINOMA
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BACKGROUND: Hyperactivation of Hedgehog (HH) signaling causes both sporadic and inherited Basal Cell Carcinoma (BCC). The inherited form of BCC, Basal Cell Nevus Syndrome (BCNS) is an autosomal dominant disease in which patients have only one functional allele of PATCHED 1 (PTCH1). PTCH1 protein represses HH signaling and loss of function leads to BCC and the childhood brain cancer, medulloblastoma. BCNS patients develop multiple BCCs and a subset (5%) develops medulloblastoma. Similarly, Ptch1 heterozygous (+/-) mice develop BCC and approximately 10% develop medulloblastoma. The retinoid, tazarotene, effectively inhibits the development of BCC in the Ptch1+/- murine model of BCC. Tazarotene specifically activates retinoic acid receptors (RAR)ß and .. RARs heterodimerize with retinoid X receptors (RXRs) to regulate retinoid target genes. OBJECTIVE: We tested whether tazarotene could inhibit medulloblastoma using the Ptch1+/- murine model in which all mice develop the cancer. METHODS: Ptch1+/- mice were exposed to a single dose of X-rays at birth and tazarotene (10 mg/Kg) or vehicle was administered daily (5x/week) from age 2.5 months. RAR and RXR expression in murine tissue samples were analyzed by immunohistochemistry. In addition, we have tested whether tazarotene therapy combined with a HH pathway inhibitor cycloamine could have a synergistic effect against BCC carcinogenesis. Though both agents can inhibit BCC independently, a BCC cell line, ASZ001, was treated with tazarotene or cycloamine alone, or in combination. RESULTS: After 7 weeks of tazarotene treatment, compared to vehicle treated mice, no significant difference in survival was observed (p=.2324). In skin, BCC and medulloblastoma samples, we found that RXRs and Gli1 were highly expressed; RARa was expressed at lower levels, while RARa and Gli1 were slightly expressed in some samples but not others. After 48h, using the WST1 Cell Proliferation assay, the combined treatment at the suboptimal concentration (5 µM) resulted in the greatest reduction of cell proliferation compared to individual treatments and combined treatments at the lower dose. CONCLUSIONS: We speculate tazarotene's ineffectiveness against medulloblastoma was due to 1) unresponsiveness of the cancer to the drug or dosage 2) drug penetration problems across the blood-brain barrier; or 3) whether the RARs and RXRs are present in the tumors. Initial results from combination therapy suggest the use of combined therapy against BCC.
Poster 13
PASSIVE IMMUNOTHERAPY FOR THE TREATMENT OF CUTANEOUS AMYLOIDOSIS
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Background: Amyloid is a fibrillar proteinacious material that is deposited in the tissues in a large variety of clinical contexts; in the skin it can be found with or without systemic disease. Primary cutaneous amyloidosis defines those amyloidosis restricted to the skin without involvement of other systems. Several treatments have been proposed to improve the cosmetic appearance of the lesions including surgical excision, carbon dioxide laser, cryotherapy, dermabrasion, curettage, and electrocoagulation. But the recurrence rate in certain types of cutaneous amyloidosis is high; therefore there is not an effective treatment to date. Objectives: Immunotherapy is a reliable method to physically remove amyloid-like aggregates in many amyloid related diseases such as Alzheimer's disease, Parkinson's disease and Diabetes. We will test the efficiency of passive immunotherapy using anti-amyloid specific antibodies, “conformational antibodies” that we developed in our lab. Our antibodies have the ability to recognize aggregated protein independent of the amino acid sequences. We want to use our antibodies to treat cutaneous amyloidosis in animal models developed, using a well established protocol by Westermark et al. Methods: After the production of the mouse model, we will perform intra-dermal injections of the conformational antibodies to elicit an immune response to the aggregates, and their removal. The efficacy of the treatment will be evaluated using immunohistochemistry and biochemical techniques. Results: We have been able to generate and extract Amyloidosis enhancing factor (AEF) from the liver of AA amyloidosis mouse models. We were able to generated cutaneous amyloidosis in Wild type mice after the intra-dermal injection of the AEF and silver nitrate and we characterized this model using conformational antibodies. Conclusion: In our studies we were able to generate and characterize a novel mouse model of cutaneous amyloidosis that will give us the possibility to evaluate the effectiveness of passive immunotherapy using conformational antibodies to remove the aggregates and restore the skin appearance in animals. This approach has previously shown great results in other amyloid related diseases.

Poster 14
COMPARISION OF MECHANICAL VENTILATION REGIMEN IN PRE-TERM INFANTS WITH RESPIRATORY DISORDERS
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BACKGROUND: The respiratory problems in neonates, particularly pre term, play a high role in mortality and morbidity rate. AIM: To analyze outcomes in pre term infants who were admitted to neonatal intensive care unit with respiratory disorders. MATERIALS AND METHODS: The study was conducted in neonatal intensive care unit of Kharkiv Regional Hospital. Retrospective analyses of total 27 pre term infants were included in the study. Out of 27 neonates 12 (44%) died and 15(55%) survived categorized as I and II groups. The study was carried out focusing on maternal anamnesis, character of delivery, course of neonate disease, mechanical ventilation (MV) regimen were postulated the results (apparatus SLE 2000 and Bear-750). RESULTS: The I group of mean birth weight 2640±480 grams with mean gestational age 24±17 weeks, and in II group of mean birth weight 2710±410 grams with mean gestational age 28±37 weeks. There were differences between maternal anamnesis such as: multiple pregnancy - 26% (I) and 9 % (II); preeclampsia - 26% (I) and 36% (II), placental abruption - 46% (I) and 27% (II), cesarean section - 53% (I) and 45% (II). After birth severe asphyxia (0-3 by Apgar) was in 60% neonates first group, and only in 9% neonates second one. Character of clinical course was following: all patients had severe respiratory insufficiency; clinic of brain edema was in 86% infants I group and 36% II group. Post hypoxic intracranial hemorrhage was diagnosed in 93% newborns I and in 27% newborns II. CONCLUSION: The multiple pregnancy, placenta abruption, severe asphyxia and intracranial hemorrhage, hypoxic ischemic encephalopathy, more frequently were in neonates with respiratory disorders who had unfavorable outcomes in our study and may be estimated as death predictors.
Poster 15
OUTCOME OF CYTOLOGY AND PATHOLOGY REVIEW OF DISCORDANT CERVICAL CANCER SCREENING EVALUATIONS
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Background: Pap smears are easy to perform and are obtained in a number of clinical settings. However, the identification of women who are at risk for having a significant cervical abnormality can be difficult. The American Society for Colposcopy and Cervical Pathology (ASCCP) has developed guidelines to be used in the management of women with cervical cytological abnormalities. The finding of high-grade squamous intraepithelial lesion (HSIL) on Pap smear carries a high risk for significant cervical disease. However, there are 32-45% of women with HSIL Paps who will have low grade cervical intraepithelial neoplasia (CIN 1) or no dysplasia on biopsy, defined as discordance. The ASCCP guidelines give review of material, a diagnostic excisional procedure or observation as acceptable options for patients with discordance. Although cervical excision procedures, such as a loop electrosurgical excisional procedure (LEEP), have been effective in the treatment of cervical lesions, it carries the risk of obstetrical complications. Objective: The purpose of this study was to determine the clinical usefulness of cytopathologic review of discordant cervical dysplasia screening cases in the determination of management recommendations in a large dysplasia clinical service. Methods: 53 patients from UTMB regional dysplasia clinics underwent multidisciplinary cytopathology review for discordance. Follow up data was obtained for 1 year. This study group was also compared to a group of patients who received a diagnostic LEEP in the absence of review. Results: 79% of patients had a change in diagnosis following review. Of the group of patients who were recommended for LEEP, 76% had high grade dysplasia. From the group that was recommended for surveillance and not a LEEP procedure, 90% had no or low grade dysplasia. There were 59% of patients with CIN 2,3 disease in the group that was not a part of the review. Conclusions: The review process lowers the number of LEEPs for discordance by 60 % with low risk of under treatment. With review, clinicians are better equipped to make treatment decisions that are appropriate, reserving LEEP for confirmed severe disease or unresolved discordance. Further study is required to define the population best served by cytopathologic review.

Poster 16
TWO-YEAR POST-OPERATIVE OUTCOMES OF ARTHROSCOPIC DOUBLE-ROW ROTATOR CUFF REPAIR
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Background: Rotator cuff tears are a common cause of shoulder pain in patients over fifty, and the associated decrease in strength and range of motion (ROM) necessitate repair. Double-row rotator cuff repair (DR RCR) involves medial and lateral suture anchors at the rotator cuff footprint. Suture bridge (SB), a double-row technique variation, draws the medial sutures over the rotator cuff tendon to lateral knotless anchors. In SB and non-suture bridge (NSB) techniques, improved healing of the rotator cuff is the ultimate goal. The purpose of this study was two-fold: (1) to report patient functional outcomes and MRI (to assess tendon healing) in the entire cohort at >2 years post DR RCR and (2) to compare outcomes of SB versus NSB configurations. Methods: Pre- and post-operative surveys included Simple Shoulder Test (SST), Visual Analog Pain Scale (VAS), American Shoulder and Elbow Surgeons shoulder score (ASES), Cumulative Activities of Daily Living score (ADL) and Constant-Murley score (C-M). Physical exam by an independent examiner measured ROM and strength (using an Isobex). Results: Thirty patients, consisting of 20 (66.7%) NSB and 10 (33.3%) SB configurations, followed up at an average of 3.3 years (1.8-4.6). Patient age was 58.4 years (35.8-80.7 years) at time of surgery. Time elapsed between symptom onset and date of surgery was a median of 7.8 months (1.7-300 months). Average tear size was 3.2 cm (2.0-6.0 cm). All subjective scores (SST, VAS, ASES, ADL) improved (p<0.05). Pain scores decreased (p<0.0001) from 5.13 to 0.90. Average (C-M) increased (p<0.0001) from 48.04 to 78.30. ROM increased (p<0.05) for forward flexion, abduction, and external rotation. Internal rotation showed a trend in improvement (p=0.0503). Strength testing in forward elevation increased (p<0.0001) from 2.42kg to 5.69kg. Postoperative MRI obtained at an average of 39.8 months demonstrated a 25% re-tear or failure to heal rate. There were no significant differences in outcomes for NSB versus SB techniques. Conclusion: Arthroscopic double-row technique is successful in decreasing pain and increasing functional outcomes in patients with full-thickness rotator cuff tears. DR RCR increases the pressurized contact area of the rotator cuff footprint to allow for better tendon-to-bone healing, and this study supports this concept from a clinical standpoint. SB did not reveal superior outcomes compared to NSB; however, additional patients and longer follow-up may reveal differences
Poster 17
PREDICTING OUTCOMES IN TOTAL SHOULDER ARTHROPLASTY USING 3-DIMENSIONAL COMPUTER SIMULATIONS
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Background: Total shoulder arthroplasty is a highly effective treatment for advanced glenohumeral (GH) arthritis. In arthritic shoulders, the normal GH anatomy becomes deformed, and symptoms can be debilitating. Characteristic radiographic findings include increased retroversion, joint space narrowing, either concentric or eccentric glenoid wear, and reactive osteophytes. These changes are unique for each patient; thus, preoperative assessment of glenoid morphology is critical to determine if glenoid prosthetic implantation is feasible. Objective: To demonstrate how varying the angle of implantation, as well as the anteroposterior (AP) and superoinferior (SI) orientations, affects the chances of a successful procedure. Methods: Axial CT scans of 20 shoulders were loaded into Mimics software, and 3D models of each patient's scapula were created. The models were then imported into custom software written in Mathematica, which three blinded observers each used to measure version angle, AP glenoid length, SI glenoid length, and mediolateral scapula length. These measurements were used to create a 3D coordinate system on the glenoid face, upon which the virtual implants were placed. Several parameters were varied, including the size of the implant, the angle of implantation, and translation along the AP and SI glenoid face. The resultant position of the glenoid implant was characterized as 1) complete containment, 2) overhang present, 3) peg penetration present, and 4) both overhang and peg penetration present. Results: Interobserver comparison showed an average $R^2$ value=0.9954 for all measurements. Frequency of incomplete containment for all geometric parameters was higher in women than in men ($p = 0.04$). AP translation to compensate for peg penetration resulted in a higher frequency of overhang. Superior translation generally resulted in higher frequency of complete containment than did inferior translation. Conclusions: We found that implant compromise is related to geometric manipulations of the implant on the glenoid face, which can influence the surgeon's preoperative and intraoperative planning. To our knowledge, there are no studies that quantify the relationships between angulation, overhang, peg penetration, or volume removed and premature implant loosening. Further studies using finite element analysis will quantify these relationships and potentially lead to increased implant durability.

Poster 18
RADIATION-INDUCED INFERTILITY: A CONCERN IN HETEROTOPIC OSSIFICATION PROPHYLAXIS?
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Background: Heterotopic ossification (HO) is a significant complication following arthroplasty of the hip in up to 25% of patients. Prophylactic radiotherapy is more effective at lowering the incidence in comparison than indomethacin; however, there is a concern for oligospermia or permanent sterility following radiation therapy for hip HO prophylaxis. While doses of less than 10 cGy resulted in no microscopic or hormonal evidence of oligospermia, doses of 10 - 50 cGy have resulted in temporary oligospermia. Permanent sterility occurs at doses greater than 350 cGy. Objective: To determine the dose to the testicles during a typical prophylactic treatment for HO and to assess the resultant risk to fertility. Methods: We randomly selected ten male pelvic CT scans from our clinical database, and excluded one due to poor visualization of the testicles. After contouring the right testicle on each of the remaining scans, we created AP/PA treatment plans to the right hip using 6MV, 10MV and 18MV beams for each patient. Field sizes ranged from 10 cm x 7 cm to 12 cm x 7.5 cm. Results: The median field size was 11 cm x 7.5 cm and the median patient thickness was 20.6 cm. Analysis of the dose volume histogram revealed the maximum and mean doses to the right testicle. The maximum doses for the 6MV, 10MV and 18MV photon beams were 21.1 cGy, 17.3 cGy and 16.4 cGy, respectively. The median doses from the 6MV, 10MV and 18MV photon beams were 8 cGy, 6.2 cGy and 5.9 cGy, respectively. With the 10MV or 18MV photon beam, the dose to the right testicle was less than 1% of the prescribed dose. However the 6MV photon beam resulted in doses greater than 1% of the prescribed dose. Conclusion: There was no increased risk of permanent sterility with HO prophylaxis. One of the 27 plans resulted in a mean testicular dose above 10 cGy, yielding a risk for clinically significant oligospermia after HO prophylaxis of 3.7%. Furthermore, higher energy photon beams resulted in less scatter radiation to the testicles.
Poster 19
COMPARISON OF TOPICAL ANESTHESIA VERSUS PLACEBO PRIOR TO KNEE INJECTIONS
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BACKGROUND: Knee injections are a common practice in musculoskeletal outpatient clinics as a treatment modality for a variety of indications. Patients who have symptomatic knee arthritis, meniscus tears, cartilage defects, and other conditions may receive intraarticular knee injections of steroid as well as other injections, such as viscosupplementation. To our knowledge, no study has been conducted to evaluate the efficacy of a topical anesthetic for pain reduction prior to intraarticular knee injections. OBJECTIVE: Our objective was to evaluate the efficacy of a topical spray anesthetic (ethyl chloride) in reducing the pain associated with intraarticular knee injections compared with the use of a saline spray as a placebo. METHODS: A prospective, single-blind, randomized controlled clinical trial. Patients who were scheduled to receive intraarticular knee injections were randomly placed into either control group A who received a placebo spray prior to their injection or experimental group B who received the topical ethyl chloride spray. Minimal selection criteria were utilized. Prior to the injection, patients were asked to assess their anticipated level of pain using a 100mm VAS scale to serve as a baseline. After the injection, patients were then asked to rate their actual pain at the time of the injection using the VAS scale. Statistical methods, T-tests, and regression analysis were then used to study the VAS scores between within each group and between the two groups. RESULTS: A total of 35 patients were included in the study, 22 in the control group and 13 in the experimental group. There was a trend indicating that those in the experimental group who received the beforehand topical ethyl chloride had less actual pain prior to the injection. The ethyl chloride group also had significant lower actual pain scores compared to their anticipated pain scores. Additionally, patients receiving their first injections reported less pain than anticipated related to the injection. CONCLUSIONS: The use of topical ethyl chloride spray is a safe and possibly may be an effective measure in reducing the pain associated with intraarticular knee injections. Furthermore, patients can be reassured that the actual pain of their first intraarticular knee injections is significantly less than anticipated.

Poster 20
MORPHOMETRY BASED PERIPHERAL NERVE SURGERY DEVELOPMENT
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Background: Patients with tibialis anterior muscle paralysis and secondary foot drop, have limited treatment options. Nerve reinnervation, the ideal solution to restore foot function, is however an unexplored option that requires histomorphometrical optimization matching between possible donor nerves (lateral soleus, lateral and medial gastrocnemius) and the tibialis anterior nerve distant to the site of injury. Objective: To explore the anatomical feasibility of using motor nerve transfer to reinnervate injured common peroneal nerves (resulting in a foot drop) and restore motor function to paralyzed tibialis anterior muscles. Methods: Ten donated cadaveric legs were studied. The specific sciatic nerve branches evaluated as possible transfers included the medial gastrocnemius, the lateral gastrocnemius, and the soleus. For histological studies, nerves were sampled at a distance needed to reach the tibialis anterior nerve using an interosseous route between the tibial and peroneal bones (UH and MPC). The transversal sections of nerves were embedded in paraffin, sectioned at 5 micron thickness, and stained with PAS and myelin (silver) stains. The number of axonal fascicles and axons were counted and their diameters were measured using the NIH J scope software (LB) and results analyzed by a pathologist (DT). Results: All nerve transfers were accomplished using a direct interosseous route and a direct end-to-end repair. The distance from the repair site to the TA muscle was shortest for the transfer using the nerve branch to the soleus. Statistically, the soleus nerve branch was most similar to the branch to the tibialis anterior for number of fascicles, axonal count and cross-sectional area. A two-incision surgical approach using a fibular window (mobilizing a fibular segment after double osteotomy) and interosseous routing of the transfer nerve is the best surgical approach. Conclusion: The reinnervation of the anterior tibial muscle using branches of the soleus nerve is feasible through an interosseous transfer route. This new technique is in use at Texas Tech University.
TYPE II ODONTOID FRACTURES IN THE ELDERLY: SURGERY VS. CONSERVATIVE MANAGEMENT

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Byron Stephens (Home institution) - University of Tennessee College of Medicine, Memphis, Tennessee; Study Institution - Saint Louis University School of Medicine, Saint Louis, Missouri.

BACKGROUND: Odontoid fractures are the most common cervical spine fracture for patients over age 70 and the most common overall spinal fracture for patients over age 80. Type II odontoid fractures are the most common sub-type and remain controversial in terms of treatment options. While many studies have examined management options looking at all types of odontoid fractures, there is a paucity of studies focusing on type II fractures.

OBJECTIVE: To compare the clinical outcomes of elderly patients with type II fractures treated non-operatively with those treated with odontoid screw fixation in terms of mortality, morbidity, and clinical healing of the fracture.

METHODS: We reviewed 20 patient charts over the age of 60 treated at a single institution for type II odontoid fracture. 11 of our patients were treated non-operatively and 9 were treated surgically. Outcomes were measured by comparing mortality, final degree of fracture angulation, and incidence of pulmonary embolism, pneumonia, myocardial infarction, and urinary tract infection. RESULTS: There were 2 deaths in our conservatively managed group and 1 in our surgically managed group. The incidence of UTI in the non-operative and operative groups was 27% and 11%, respectively. 1 conservatively managed and 2 surgically managed patients developed pneumonia. There were no MIs or PEs in either group. Falls were the mechanism of action for all the surgical patients, whereas the conservatively managed group had 5 MVAs and 6 falls. The final degree of posterior angulation of the odontoid was significantly greater in the surgically managed patients, but not clinically limiting. CONCLUSIONS: In this small descriptive study, the overall clinical results were similar between our groups. Complications with immobilization in our study were not consistently defined but have been noted to be significant in the literature. The increased mortality rate in the non-surgical group as well as the fact that falls were the only mechanism of injury in the surgical group may reflect surgical selection bias. In the operative group, there was a slight posterior tilting of the odontoid at follow-up that was not clinically limiting and most likely can be attributed to osteopenia. In our study there was no evidence of failure of odontoid screw fixation in the elderly and this continues to provide a safe option for those patients not wanting to undergo immobilization for type II odontoid fractures.

MR1 EVALUATION OF TERES MINOR HYPERTROPHY AND FUNCTIONAL STATUS IN PATIENTS WITH MASSIVE ROTATOR CUFF TEARS

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Background: Loss of shoulder function in patients with rotator cuff tears (RCT) is variable and not well understood. While many patients with massive RCT present with loss of active shoulder motion, other patients maintain mobility. One theory that accounts for maintaining active motion is related to axial plane balance of the anterior and posterior cuff musculature. Hypothesis: In the setting of massive tears, preservation of axial plane balance requires maintenance or hypertrophy of the teres minor muscle. Methods: This study correlates radiographic evidence of teres minor hypertrophy in patients with RCT with clinical function assessed via patient-centered questionnaire (Simple Shoulder Test), physical exam findings, and shoulder range of motion. Patients are divided into those with (1) evidence of massive RCT retaining the ability to actively forward elevate (FE); (2) evidence of massive RCT lacking the ability to FE; and (3) no radiographic evidence of RCT but evidence of SLAP tears, impingement, or shoulder instability. Retrospective data from 60 patients were collected. The cross-sectional areas (CSA) of shoulder musculature were calculated using 3D MRI reconstruction. Teres minor CSA was compared to subscapularis CSA and total rotator cuff CSA. Results: Patients with RCT maintaining FE had a higher teres minor/rotator cuff ratio and a higher teres minor/subscapularis ratio than both other groups (p < 0.001). Simple Shoulder Test scores (higher score indicates better subjective function) for patients with RCT maintaining FE were similar to patients with no RCT, and higher than patients with poor FE (p< 0.0173). Conclusions: Patients with relative hypertrophy of the teres minor maintained active range of motion and reported better overall subjective function. The results of this study provide a better understanding of cuff musculature and balance and may lead to improved therapeutic interventions and pre-operative planning. A prospective arm is underway and will include cuff muscle volumes obtained from MRI and strength measurements from isometric dynamometry.
Poster 23
AUTOFLUORESCENCE IMAGING OF THE RETINAL PIGMENT EPITHELIUM TO MONITOR BENEFITS OF INDUCED HSP UPREGULATION IN RESPONSE TO PHOTOTHERMAL DAMAGE
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Purpose: Autofluorescence imaging using a modified confocal scanning laser ophthalmoscope (SLO) provides a sensitive, non-invasive method of evaluating retinal damage incurred after laser exposure. In this study, we investigate damage to retinal tissue and wound healing in relation to the upregulation of heat shock proteins (Hsp) in a small animal model. Methods: Brown Norway rats at least 12 months of age were imaged in vivo with a modified Heidelberg Retina Angiograph (HRA I) to obtain images of the fundus by autofluorescence at 488 and 514 nm. Hyperthermia was induced in the rats to upregulate Hsp synthesis by submerging the animals in a water bath at 42°C. The rectal temperature of each animal was monitored to insure that core body temperature remained above 41°C for 20 minutes. A Coherent Ultima argon-ion laser operating at 514 nm was used to create photothermal damage with an exposure time of 100 ms and a 0.10 mm spot size to photocoagulate the retina of pigmented rats. Results: Exposure to 514nm light caused an immediate decrease in autofluorescence enabling retinal lesions to be monitored for weeks after they were no longer visible with white light fundoscopy. Upregulation of Hsp synthesis was induced 18 hours prior, 4 hours prior, and immediately after laser exposure. Follow-up imaging at one week and two weeks showed evidence of less sustained retinal damage in the group of animals receiving heat treatment immediately after laser exposure. Conclusions: SLO imaging provides unique capabilities enabling non-invasive evaluation of changes in biochemical composition of retinal tissue and wound healing in the retina. The dynamic effects of induced Hsp upregulation can be observed to have the greatest effect immediately after laser exposure. It is conceivable that induction of Hsp synthesis could have therapeutic applications in treating retinal damage due to sudden laser exposure.

Poster 24
AN EVALUATION OF LUNG MECHANICS DURING COMPUTER ASSISTED WEANING
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Background: The ability to quickly and successfully wean patients from mechanical ventilation is vital in the ICU to prevent nosocomial infections and associated morbidity and mortality. In prior studies, two methods of weaning have been shown to be most effective: pressure support and daily spontaneous breathing trials. Because adherence to these evidence-based weaning protocols is often poor, automated, computer-driven weaning methods have been developed. However, previous studies of computer-assisted weaning methods have not examined the lung mechanics during automated weaning and have yielded conflicting results as to whether automated weaning programs shorten weaning duration. Objective: To evaluate differences in lung mechanics during weaning from mechanical ventilation in patients randomized to computer weaning compared to standard care weaning. Only lung mechanics were evaluated during this preliminary analysis. No data on weaning times or clinical outcomes was accessed for this analysis. Methods: This is a sub-study of an ongoing randomized, controlled trial comparing computer directed weaning (CDW) using the Draeger Smartcare/Pressure Support system with standard care weaning (SCW) consisting of pressure support weaning or daily spontaneous breathing trials. Lung mechanics (respiratory rate, tidal volume, end tidal CO2, and pressure support) were recorded every four hours, beginning at the onset of weaning for the first 20 study participants. Results: Ten patients were randomized to each group. Baseline data showed no difference in age, sex, race, BMI, APACHE II score, lung injury score, or reason for intubation between the two groups. Compared with SCW, the CDW group was weaned with a significantly smaller average tidal volume (423 ± 134 vs. 508 ± 148 ml, p=0.0005) and a trend towards an increased respiratory rate, (22.3 ± 4.7 vs 20.9 ± 4.9 breaths per minute, p=0.07), without a difference in average end tidal CO2 (37.5 ± 7.6 vs 36.6 ± 10.7 mmHg, p=0.6) or level of pressure support (7.3 ± 4.6 vs 8.1 ± 2.7 cmH2O, p=0.2. Conclusions: This preliminary analysis demonstrates that the CDW system weans patients utilizing lower mean tidal volumes compared with SCW. These differences in weaning mechanics might explain the shortened weaning duration seen in one prior study of CDW. Future research should focus on correlating these differences in lung mechanics with differences in clinical outcomes such as weaning time, length of ICU stay, and mortality.
Cardiomiopathy contributes to the high incidence of cardiac dysfunction in diabetes mellitus although the mechanisms involved are unclear. Most of the studies that investigate these mechanisms use whole heart or single cardiomyocytes. However, little is known about the significance of coronary microvascular endothelial cells in diabetes cardiomiopathy. The development of diabetic cardiomiopathy may result partly from altered intracellular Ca2+ homeostasis in endothelial cells. The Na+/Ca2+ exchanger (NCX) is considered to be the dominant calcium efflux mechanism in cardiac myocytes. It is unclear, the significance of NCX for [Ca2+]cyt regulation in endothelial cells. To understand the mechanisms involved in diabetic cardiac dysfunction, we used coronary microvascular endothelial cells to study [Ca2+]cyt homeostasis in response to stimulation by ATP, ouabain and palytoxin. The significance of NCX was evaluated using ion substitution and silencing RNA approaches. We isolated endothelial cells from the ventricles of type 1 diabetic BB rat; and aged-matched, non-diabetes-prone BB rat. [Ca2+]cyt was monitored by fluorescence based spectroscopy using fura-2. Our data indicated that the NCX operates to maintain [Ca2+]cyt elevated and prolonged in normal endothelial cells upon ATP stimulation, i.e. reverse mode. However, in diabetic cells, NCX operates to extrude Ca2+ out of the cell, i.e. forward mode. These data suggest the presence of a molecular switch that is responsible for the alternate activity of the NCX between normal and diabetic endothelial cells. This molecular switch is a novel pharmacological target that could be used to alleviate the consequences that lead to diabetic cardiomiopathy.
Background: NASA's future goals include missions to the moon which will require extended exposure to the lunar (1/6) gravity environment. To prepare for these missions, physiological adaptations in various systems must be resolved. We have used bed rest at a 9.5° head-up tilt to simulate lunar gravity. Plasma volume index (PVI) is used to determine the magnitude and time course of fluid shifts and cardiovascular adaptation to 1/6G. The Digital Astronaut, a computer simulation tool, predicts a 6% PVI loss during an extended simulated lunar mission for a male with a body surface area of 1.95 m². Simple geometry suggests that 9.5° head-up tilt is most useful to measure deconditioning in bone and muscle. However, 2° head-up tilt may best simulate cardiovascular fluid shifts. In order to reconcile these different models, compression stockings must be used in the 9.5° paradigm to better approximate expected cardiovascular fluid changes. Objective: Evaluate the effectiveness of knee-high and thigh-high stockings for fluid redistribution in the lunar bed rest analog based on Digital Astronaut computer model predictions. Methods: Subjects arrived at the unit three days prior to beginning bed rest and were acclimated to the controlled diet. The baseline PV was taken at 6pm one day prior to beginning bed rest (BR-1). Subjects remained at a 9.5° head-up position for 6 days followed by a PV measurement 6pm (BR+6). Knee-high and thigh-high stockings were worn from 6am to 10pm. Efficacy of the stockings was determined by the average PVI (PVI/BSA) which most closely approximated the Digital Astronaut model prediction. A two-sample student t-test assuming equal variances was used to determine the difference between the two stocking types. Results: Combined PVI is decreased by 10.80% (SE ± 3.25) during head-up bed rest. The knee-high stockings resulted in a PVI decrease of 9.72% (SE ± 8.33) while the thigh-high stockings decreased 11.7% (SE ± 3.22). There was not a significant difference between the two stocking types (p = 0.83). Conclusions: PVI losses confirm the value of this model of lunar gravity for fluid shifts predicted by the Digital Astronaut. There were no statistical differences between stocking types. Subject comfort and compliance were enhanced by use of the knee-high stockings; therefore, knee-high stockings will be used in further lunar bed rest studies.

Poster 28  
**SURVEY OF DEMOGRAPHICS AND DIAGNOSES OF PATIENTS TO ASSESS PREVALENCE OF KNOWN HIV STATUS, ARV USE AND COMPLICATIONS, AND CLINICAL AIDS DIAGNOSIS IN PARIRENYATWA CENTRAL HOSPITAL IN HARARE, ZIMBABWE**

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Background: Surveillance and data collection is challenging for the Zimbabwean healthcare community. Scarce resources keep focus on treatment rather than epidemiology. There is limited data on HIV/AIDS prevalence, antiretroviral (ARV) use and tuberculosis (TB) infection rates. Data gathered in this study could help with healthcare planning and to optimize division of resources. Objective: to determine the prevalence of HIV/AIDS in a cohort of patients admitted to an adult medical ward, the access to and acceptance of HIV testing, and disease presentation in the HIV infected versus non-HIV infected patients. Methods: 255 patients admitted to the adult medical ward at Parirenyatwa Central Hospital Harare, Zimbabwe were surveyed. Information such as demographics, medical history, presenting symptoms, admission diagnosis, medications, HIV status, HIV testing and ARV use was obtained via personal interview. A translator was used when patients preferred to speak Shona, and informed consent was provided in the patients’ preferred language. IRB approval was obtained from the home institution and from the University of Zimbabwe Medical School. Results: Estimated HIV prevalence in this population was 52.9% (135/255 patients). This includes 76 patients previously testing HIV positive (known HIV +) and 59 patients without a known prior positive test but a presenting condition compatible with WHO clinical stage 3 or 4. Of the 124 patients who had previously been tested for HIV, 76 were HIV+, 33 were HIV (-) and 15 did not know their status. Of the known HIV+ patients 31 had ever received ARVs, and 11 were scheduled to receive them. 93 patients were eligible for ARVs by clinical stage criteria but had never received them. There were 39 cases of TB, not including rule-out cases. TB prevalence was highest in HIV + cases (26.3%) compared to HIV (-) cases (8.8%), and to those never tested, tested but did not know the result, or did not reply to the question (11.4%). 92.3% TB patients were co-infected with HIV. Conclusions: There is high prevalence of HIV infection and co-infection with TB in medical inpatients. Less than a third of those eligible for receiving ARVs had ever received them, or were scheduled to begin treatment. Future studies would determine whether the characteristics described in this population are representative of the larger population, what the differences are between rural and urban hospitals, and between private and government hospitals.
Poster 29

ALCOHOL USE DISORDER SCREENING IN EMERGENCY GENERAL SURGICAL PATIENTS: A COMPARISON OF TWO SITES
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Background: The acute care surgical movement has led to services that combine emergency general surgical (EGS) and trauma patients. Alcohol use disorder (AUD) screening and brief interventions (SBI) are already an accepted part of trauma care and has become increasingly common for those requiring emergency services. With growing recommendations and incentives for SBI in all patients - by the American Medical Association, the National Quality Forum, and others, extending SBI to EGS services may seem warranted. However, given the resources needed for SBI, we questioned this notion. Our hypothesis was that significant variability would exist between different EGS services, making automatic expansion of SBI inappropriate in some cases. Methods: Patients from two Level 1 trauma centers, sites A and B, admitted to EGS services that were 18+ years old were queried face to face about alcohol use with standard screening questionnaires. Exclusion criteria were admission <24 hours, altered mental status, lack of English fluency, or other inability to answer questions. Patients at site A were also queried about their willingness to discuss AUD while hospitalized. Results: One hundred five patients were approached in total, and 2 declined. Overall, 43.7% (n=45) were nondrinkers. Only 11 (10.5%) met the criteria for “risky drinking,” but prevalence varied by site (site A: 9.8%, site B: 23.1%, (p=.014)). Moreover, at site A, only 3.3% of patients binge drank greater than monthly, compared to 15.4% at site B (p<.001). At site A, 82% had a primary medical doctor and only 8.8% had no health insurance in contrast to site B, where 60% had no health insurance (p=.001). Fifty of the patients at site A were sampled for their willingness to discuss AUD. The majority stated that it would be OK for a physician to discuss alcohol (94.2%) or to have brief counseling offered while in hospital (93.9%). Conclusions: EGS patients are willing to discuss alcohol use while in the hospital. However, unlike trauma patients, the prevalence of AUD is highly variable and low at some sites. A low prevalence would not warrant the additional resources required for automatic expansion of an SBI program. Prior to service expansion, the institution’s prevalence of AUD among EGS patients should be examined. At some centers, these patients could otherwise be captured in a primary care setting.

Poster 30

EXAMINATION OF PATIENTS’ WEIGHT REDUCTION EXPECTATIONS AND DESIRE FOR CO-MORBIDITY RISK REDUCTION PRIOR TO BARIATRIC SURGERY
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Background: Research examining weight loss expectations preoperatively in bariatric surgery patients has demonstrated unrealistic goals. Additionally, patients' motives in undergoing surgery need further exploration. Objective: The purpose of this study was to explore bariatric patients' expectations with respect to weight loss, as well as management of medical co-morbidities. Methods: Data was collected prospectively on 45 consecutive patients who were scheduled to undergo weight reduction surgery. Participants completed a modified Goals and Relative Weights Questionnaire GRWQ assessment battery 1 week prior to their anticipated surgery. Results: A total of 45 patients completed the survey (Gastric Banding (LAGB) 23/45; Gastric Bypass (RNYGB) 22/45). The mean goal weight loss of the 45 patients was 118.5 +/- 65.9lbs. The mean goal excess weight loss (EWL) of the 45 patients was 85.0% (range 21%-127%). Moreover, LAGB and RNYGB had mean EWL of 80.2% (21%-127%) and 90.5 % (37%-130%) respectively (p=0.38). Of 13 possible satisfaction factors that we included in our questionnaire, "a desire for change in medical co-morbidities," was deemed as most important (10=most important 1=not important) in choosing a goal weight. Interestingly, patients rated, "a desire for change in medical comorbidities," with a mean and standard deviation of 9.51 +/- 1.1; LAGB: 9.8+/-0.7; RNYGB: 9.4 +/- 1.2). On the other hand, parameters such as social acceptance, spouse and family perception were ranked lower compared to an improvement in medical co-morbidities. Conclusion: The results of our study demonstrate that candidates for bariatric surgery display unrealistic weight loss expectations for bariatric surgery. Nonetheless, bariatric surgery patients possess knowledge regarding beneficial effect of bariatric surgery on co-morbidity resolution but hold lowered expectations with regards to the anticipated effect their operation will have on their current disease states. Additional studies are needed to determine the source of the unrealistic expectations and how they influence long-term outcomes.
Determinants of Adequate Follow-up of an Abnormal Papanicolaou Result Among Jamaican Women in Portland, Jamaica

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Background: Cervical cancer is the second most common cancer among women worldwide. Among Jamaican women, cervical cancer is the second leading cause of cancer mortality. Screening for cervical cancer through Papanicolaou (Pap) smear is the first step and the best way towards preventing morbidity and mortality. However, failure to adequately follow-up with testing and treatment defeats the initiative of screening and intention to prevent cervical cancer. Furthermore, factors that facilitate follow-up of Jamaican women receiving abnormal Pap smear results are not known. Objective: We examined whether socio-demographic factors, factors reported by the women, and assistance received for follow-up facilitated adequate follow-up of abnormal Pap smears. Methods: One hundred-and-twenty-one women who had abnormal Pap results during June 1998-September 2005 in Portland, Jamaica were interviewed to identify determinants of adequate follow-up. Chi-square, t-test and multivariable logistic regression analysis were used to identify determinants. Results: Only half of the women in this sample sought adequate follow-up. These women had lower number of surviving children, higher monthly income, and thought that cost of services was inexpensive. In contrast, more than half (56.6%) of the women who did not receive adequate follow-up action thought that the cost of services were expensive, with statistically significant association between cost of services and follow-up action (p<0.05). Advice about the timing of the follow-up activity and the next step to take were significant determinants of adequate follow-up. Women who received advice on the timing of follow-up were almost six times (adjusted OR: 5.99, 95% CI: 1.17, 30.66, p<0.05) more likely to seek adequate follow-up after adjusting for other factors. Conclusions: Low cost of services as well as assistance provided by healthcare workers regarding follow-up facilitates adequate follow-up of abnormal Pap smear results. Communication between the patient and the provider encourages the patient to seek appropriate care in the proper time frame. Finally, the timing of the recommendation and specific instructions on how to pursue follow-up care should be a major focus of any communication between the provider and the patient. Future research, including a population-based study, would be helpful in providing a clearer understanding of other factors that promote adequate adherence to follow-up care.

Numerical Literacy and the Ability to Advise Patients of Risk: Multi-Institutional Study of Medical Students and Undergraduates

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Introduction: Numerical literacy (numeracy) is a prerequisite for physicians making appropriate treatment recommendations to patients. This is especially true in an era of evidence-based medicine. Medical schools emphasize the acquisition of quantitative skills. Based on observations, we hypothesized that medical students do not uniformly appear to be numerically literate. We tested this hypothesis using a clinical scenario dependent on students’ abilities to quantitate risk. Methods: Students were recruited via a website and all responses were anonymous. After completing a validated numeracy questionnaire, participants were presented with a vignette of a patient deciding on adjuvant chemotherapy after bladder cancer surgery. Students were then asked questions to ascertain their comprehension of risk. Results: 251 medical students from Emory University, the University of Arkansas, the University of Alabama at Birmingham, and the University of South Alabama Schools of Medicine did not significantly differ in demographics. Only 72% of medical students had perfect numeracy (score=3) (mean + SD = 2.56 + 0.72), with no significant difference in numeracy across institutions (p=0.463). Additionally, numeracy did not significantly differ across academic year for all medical students (p=0.138). Consequently, 15% of medical students could not accurately assess likelihood of patient survival, with no significant difference across institutions (p=0.782) or academic year (p=0.599). Conclusions: Approximately 30% of medical students are not fully numerate. Surprisingly, innumeracy does not change through years of medical school. This may prevent students from fully understanding survival data related to therapy, which could in turn affect patient safety and care.
Poster 33

**RACE DIFFERENCES IN SELF-ASSESSED HEALTH: THE ROLE OF JOB STRAIN**

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A firmly established and frequently reported pattern in the distribution of health status in the U.S. is that non-Hispanic blacks (NHB) have higher rates of mortality, morbidity, and disability than do non-Hispanic whites (NHW). Although much research has examined the relationships between race and health many questions pertaining to the processes that lead to such persistent disparities remain. There is accumulating evidence showing that the psychosocial environment at work affects the mental and physical health of workers. Specifically, work characterized by heavy demands and low decision latitude have the greatest negative affect on health outcomes. The present study seeks to investigate the potentially mediating role work characteristics have in explaining health disparities by race. Using data from a nationally representative cross-sectional survey of U.S. non-institutionalized adults 18 years and older, a sample of NHB and NHW who were regular, permanent employees having been with their current job for at least 9 months were selected for analysis (N=2244). The outcome for this project, self-assessed health (SAH), has been shown to be a valid and reliable measure of overall health status and a valid measure across racial/ethnic groups. There is a strong association between poor SAH and morbidity, mortality, and physical disability. Logistic regression was used to determine the odds of reporting differences in SAH on a 3-item Likert scale ranging from excellent/very-good to fair/poor. Those above the median score for job demands and below the median score for decision latitude were classified as having a high strain job and were compared to three other categories; low, passive, and active strain jobs. NHB were significantly more likely to report poorer SAH (OR=1.27, 95% CI=1.03-1.58) and were more likely to be in a high strain job (OR=1.33, 95% CI=1.04-1.71) than NHW. The odds disparity by race of reporting poorer SAH was partially mediated by the addition of job strain to the model (OR=1.21, 95% CI=0.97-1.50). After adjustment for potentially confounding variables, race differences in SAH were further mediated (OR=0.91, 95% CI=0.71-1.16) while those having a high strain job remained significantly more likely to report poorer SAH compared to those with other job types. These results demonstrate that race differences in SAH can be mediated to non-statistical significance by accounting for work environment characteristics.

Poster 34

**INTRACRANIAL CATHETERIZATION USING A SACRAL HIATUS ACCESS AS AN ALTERNATIVE FOR PERCUTANEOUS INTRASPINAL NAVIGATION: A STUDY IN CADAVERS**

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Background: Intraspinal navigation with catheters and fiberscopes has shown feasible results for diagnosis and treatment of intraspinal and intracranial lesions. The most common approach, lumbar puncture, has allowed access to the spinal cord. This approach, however, comes with the difficulties of fiberscope damage and decreased torque for guidance. Our objective in this study is to demonstrate an alternate access, the sacral hiatus, into the subarachnoid and intracranial structures, with decreasing the angle of entry and improving the torque. Objective: We believe it is possible to access the subarachnoid space and basal cisterns of the intracranium through the sacral hiatus with a guide wire technique while not inflicting damage on the surrounding structures. Methods: We advanced catheters with guide wire and fluoroscopy assistance into the sacral hiatus’ of three cadavers. After entry, the thecal sac was punctured and the catheter with guide wire was advanced rostrally until positioned in the basal cisterns of the brain. We confirmed catheter placement with contrast injection followed by autopsy confirmation. Results: In our study the sacral hiatus was easily accessed, but resistance was found when attempting to puncture the thecal sac. The advancement of the catheter with guide wire assistance glided easily rostrally until mild resistance was discovered at entry into the foramen magnum. With redirection, all catheters passed with ease into the basal cisterns. Positioning was confirmed with contrast injection with fluoroscopy evidence and direct visualization at autopsy. There was no macroscopic or microscopic evidence of damage to the spinal roots, spinal cord, or cranial nerves. Conclusion: The sacral hiatus with guide wire assistance is an accessible conduit for uncomplicated entry into the subarachnoid and basal cistern space without damaging surrounding structures.
VEssel movement and image quality in the diagnosis of arterial disease with MRI

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Background: Stroke is the second leading cause of death and the most common cause of complex chronic disability worldwide. 3D Contrast Enhanced Magnetic Resonance Angiography (3D CE-MRA) is now one of the most widely used radiological methods for evaluating arterial stenosis, an important prognostic indicator for cerebral ischemia related to stroke. A potential problem with carotid 3D CE-MRA is that long acquisition times predispose the images to degradation due to carotid motion. Objectives: Although it has been hypothesized that carotid artery motion has a significant effect on 3D CE-MRA image quality, the link has not been directly tested in patients. Thus, our goal is to examine the degree of carotid artery motion and compare it to image sharpness in the corresponding 3D CE-MRA exam in patients presenting with suspected carotid artery disease. Methods: We designed an MRI protocol, utilizing an existing cinematic technique, to obtain animations of the neck near the most common site of carotid artery disease — the bifurcation of the carotid arteries. These animations were acquired from 5 healthy volunteers and 8 patients presenting for a 3D CE-MRA of the carotid arteries. A custom Matlab program was used to detect vessels and calculate their movement in the cinematic images. Another Matlab routine was used to measure vessel wall sharpness in the 3D CE-MRA images at the same locations as movement was measured. A qualitative sharpness measurement was provided by an experienced neuro-radiologist who scored 3D CE-MRA image quality on a scale of 1-4. Results: On average, across the cardiac cycle, peak-to-peak pulsation (change in cross-sectional area) was 128±8% and peak-to-peak translation was 1.79±0.77 mm. This compares closely with previously measured peak-to-peak translation: 1.44±0.43 mm. Based on current data, there is no correlation between vessel movement and 3D CE-MRA image sharpness. Conclusions: Carotid artery movement due to pulsatile blood flow varies sizably between individuals and between locations within an individual. Our data from 16 arteries (8 patients) does not show a direct correlation between carotid artery movement and 3D CE-MRA image quality. Image quality may be limited more by other factors such as contrast variation, low resolution and noise than by vessel movement. Therefore, vessel movement arising from pulsatile blood flow may not be an important factor until 3D CE-MRA image resolution has been further improved by other means.

DESIGN OF FOLIC ACID-CONJUGATED CROSS-LINKED POLYMER MICELLES FOR DELIVERY OF MAGNETIC RESONANTS IMAGING AGENTS

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Paramagnetic gadolinium(III) chelates are routinely used as contrast agents for magnetic resonance imaging (MRI) in clinical practice for detection of tumors. These agents extravasate rapidly into extracellular fluid space and have a short tissue retention time. To prolong the circulation and retention of these agents, novel multifunctional cross-linked polymer micelle carriers for active delivery of MRI agents were prepared and characterized in this study. The folate-bounded micelles can be guided to the cancer cells, because folate-binding proteins (FBP) are specifically overexpressed on the cancer cell membranes. The block ionomer complexes of poly(ethylene oxide)-b-poly(methacylic acid) copolymer and divalent metals cations were utilized as templates for the synthesis of the polymer micelles with cross-linked ionic core. The polymer micelles were conjugated with chelating agent, diethylenetriaminepentaacetic acid (DTPA) and loaded with Gd(III). The concentration of bound Gd(III) was determined by Inductively Coupled Plasma Spectrometry (ICP-MS). Relaxivity (R1) of the Gd-loaded micelles was evaluated by a progressive saturation imaging method on 7 T Bruker Avance system. Also, such micellar templates were modified by near-infrared fluorescent probe (Alexa 680) for detecting in vivo tumors. In vivo optical imaging was performed on anesthetized mice with an IVIS 200 small animal imaging system (Xenogen). The polymer micelles were conjugated to the active folic acid via PEG terminal amino groups. The specific interaction between the folate-conjugated micelles and FBP was evaluated by Surface Plasmon Resonance (SPR, BIAcore 3000). The particle size of DTPA-modified cross-linked polymer micelles was in the range of 100-120 nm. The Gd(III)-loaded micelles demonstrated good dispersion stability in phosphate buffered saline and had an ionic relaxivity of 5.2 mM-1s-1 per Gd(III) at 7 Tesla. The micelles with high content of Gd(III) exhibited a low stability at physiological conditions and a low ionic relaxivity, possibly due to steric hindrance of Gd(III) ions inside the cross-linked cores. The SPR analysis confirmed a specific binding of the folate-nanoparticles to the FBP. In conclusions, Gd-loaded cross-linked polymer micelles may be suitable as macromolecular contrast probes for MR imaging. The degree of modification of the micelles with DTPA is important parameter affecting the R1 of such materials.
DUODENAL SWITCH PROVIDES SUPERIOR RESOLUTION OF METABOLIC COMORBIDITIES INDEPENDENT OF WEIGHT LOSS IN THE SUPER-OBSE (BMI = 50 kg/m2) COMPARED WITH GASTRIC BYPASS

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OBJECTIVE(S): Increased BMI is associated with greater incidence and severity of obesity-related comorbidities and inadequate post-bariatric surgery weight loss. Accordingly, comorbidity resolution is an important measure of surgical outcome in super-obese individuals. We previously reported superior weight loss in super-obese patients following duodenal switch (DS) compared to Roux-en-Y Gastric Bypass (RYGB) in a large single institution series. We now report follow-up comparison of comorbidity resolution and correlation with weight loss. METHODS: Data from patients undergoing DS and RYGB between August 2002 and October 2005 were prospectively collected and used to identify super-obese patients with diabetes, hypertension, dyslipidemia, and gastroesophageal reflux disease (GERD). Ali-Wolfe scoring was used to describe comorbidity severity. Chi-square analysis was used to compare resolution and two-sample t-tests used to compare weight loss between patients whose comorbidities resolved and persisted. RESULTS: 350 super-obese patients (DS (n=198), RYGB (n=152)) were identified. Incidence and severity of hypertension, dyslipidemia, and GERD was comparable in both groups while diabetes was less common but more severe in the DS group (24.2% vs. 35.5%, Ali-Wolfe 3.27 vs. 2.94, p<0.05). Diabetes, hypertension, and dyslipidemia resolution was greater at 36 months for DS (diabetes, 100% vs. 60%; hypertension, 68.0% vs. 38.6%; dyslipidemia, 72% vs. 26.3%), while GERD resolution was greater for RYGB (76.9% vs. 48.57%; p<0.05). There were no differences in weight loss between comorbidity “resolvers” and “persisters”. CONCLUSIONS: In comparison to RYGB, DS provides superior resolution of diabetes, hypertension, and dyslipidemia in the super-obese independent of weight loss.

TRABECTOME ABLATION ARC CLINICAL RESULTS AND RELATION TO INTRAOCULAR PRESSURE

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Background: The Trabectome is a novel device for performing ab interno goniotomy for the treatment of open angle glaucoma. The procedure differs from traditional goniotomies in that the trabecular meshwork (TM) and inner wall of Schlemm’s canal (SC) are not incised, but ablated with electrocautery. Objective: To determine if the amount of tissue ablation is associated with the degree of intraocular pressure (IOP) lowering and reduction of glaucoma medications. Methods: Medical records of subjects who had undergone Trabectome surgery at the Mayo Clinic between Sept 2006-Aug 2007 and were at least 3 months from their initial surgery date were reviewed. Stereoscopic gonioscopy photographs were obtained for 360 degrees of the corneoscleral angle in each eye which had undergone surgery. Photographic montages were used to reconstruct a single image of the entire angle for each eye. The areas in which the TM and SC remained visibly open (ablation arc) were identified using the montages in conjunction with the stereoscopic photographs. Generalized estimating equation models were used to determine the correlation between the size of the ablation arc in degrees, and the amount of IOP lowering and reduction in number of medications. Results: Fifty-seven patients underwent Trabectome surgery between September 1, 2006 and August 31, 2007. Seven of 57 patients underwent bilateral surgery and two required a second Trabectome surgery yielding 66 unique procedures. Of these 66% were combined with cataract extraction. 28 eyes of 26 patients were photographed and analyzed. The mean ablation arc for the 28 available eyes was 87.0 ± 29.1 degrees (mean SD) at a mean of 6.9 3.3 months after surgery. The pre operative IOP was 20.4 ± 9.7 and final post operative IOP was 15.4 ± 6.1 yielding a mean decrease in IOP of 5.06 ± 9.4 (p<0.001). There was a reduction in the number of IOP lowering medications from 2.6 ± 0.9 to 1.1 ± 1.0 with (p < 0.001). There was no statistically significant the correlation between ablation arc and reduction in IOP (p=0.50) or final IOP (p=0.89). Conclusions: The amount of TM and SC tissue ablated does not significantly alter the post-operative IOP result. One explanation is that if at least partially circumferential flow in SC exists, then the size of the opening would be less important than the maintenance of a patent opening in the TM and SC. An alternate explanation is that the size of the ablation arcs fell in a relatively narrow range.
Poster 39
OUTCOMES OF SUPERIOR LABRAL, ANTERIOR TO POSTERIOR (SLAP) TYPE II REPairs
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Background: Superior labral anterior to posterior (SLAP) lesions are defects in the superior labrum along the glenoid surface. Defects often occur in athletes or heavy-duty laborers. Due to the mechanism of injury, these young patients have loss of function specific to a job or skill imperative to their daily activities. Objective: The purpose of this study was to assess the functional outcomes of patients at a minimum of two years after surgical type II SLAP repair. Methods: This was a prospective study of 46 patients with intra-operatively diagnosed SLAP II lesions that underwent arthroscopic repair. Patients with surgically treated rotator cuff tears or biceps tenodesis/tenotomy were excluded from this study. Both subjective (UCLA shoulder test, American Shoulder and Elbow Surgeons (ASES) shoulder score, Simple Shoulder Test (SST), cumulative Activities of Daily Living (ADL) score, Visual acuity pain scale (VAS), SF-12) and objective (range of motion (ROM), and post-operative strength) measurements of the operated shoulder were recorded pre-operatively and at least 2 years post-operatively. All results were analyzed using paired t-test. Results: The study population, mean age 32.0 years (15.2 to 58.9) at time of surgery, mean time period between injury and SLAP repair 0.95 years (0.09 to 3.9), followed up at mean 3.4 years (1.7 to 5.7). Pre- to post-operative comparisons were significant (p<0.05) for SST (7.32, 10.32), ASES (59.93, 81.85), VAS (3.98, 1.55), and ADL (12.32, 17.7). ROM significantly improved for forward flexion (158, 175.5), abduction (155.2, 175.0), and internal rotation (7.91, 9.45; 0-10 scale based on ability to reach specific vertebral levels). Post-operatively, UCLA revealed a mean 30.41 on a scale of 35 which, according to the test’s guidelines, indicates good to excellent results. Given their experience, 86.67% of patients said they would choose SLAP repair again if given the opportunity. External rotation and SF-12 data did not show statistical significance. Conclusion: According to these results, arthroscopic SLAP repair provides a significant improvement in pain relief and shoulder functional capacity. This study is significant in that it has a large SLAP II population, measuring subjective and objective data both pre- and post-operatively. This data supports published literature that suggests SLAP repair is an effective procedure to surgically manage pain and loss of function associated with a superior labral tear.

Poster 40
AGREEMENT OF ASSESSMENT METRICS IN THE DIAGNOSIS OF OBESITY
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Background- In assessing the extent of the current obesity epidemic BMI has been the major tool used, but it has a number of limitations as obesity is an excess of adipose tissue and not an excess of weight for height. The ACSM rates BMI and other anthropomorphic measurements, BMI is considered fair to unacceptable in terms of accuracy and only fair overall while skinfolds and bioelectrical impedance are rated higher in accuracy and overall. BMI is influenced by body proportions such as leg length for height so that individuals with shorter legs for their height have higher values of BMI and is insensitive at distinguishing between lean and fat mass and so is an ineffective measure at diagnosing obesity. If BMI is to be used in the treatment of obesity in public health and clinical practice it should agree with other metrics that more specifically assess adipose tissue. Objective-There is a difference in the rates of obesity between BMI, DEXA and Skinfolds. Methods - Data and subjects were obtained from the NHANES 03-04 dataset, 54% male and 46% female aged 20-85. Any subject who did not have data for all three metrics was excluded. Data were analyzed with SPSS with prevalence, Phi, percent agreement and Kappa generated. Cut-offs for obesity were set at > or = 30 for BMI for all subjects, >35% bodyfat for males for both DEXA and Skinfolds and >25% bodyfat for males for both DEXA and Skinfolds. Results-The rates of obesity for BMI, DEXA and Skin Folds were 20.4%, 71.7% and 10.1% respectively. Skinfolds & BMI: % agreement = 82.8%, Phi = 0.378 and Kappa = 0.348. DEXA & BMI: % agreement = 48.1%, Phi= 0.302 and Kappa = 0.174. DEXA & Skinfolds: % agreement = 38.3%, Phi = 0.208 and Kappa = 0.084. Phi and Kappa were significant at p<0.001 for all statistics. n = 3293. Conclusion-All three metric were statistically significantly correlated. There was a very large clinical difference in the rates of obesity produced by the three metrics and it cannot be said that BMI performed adequately to agree with DEXA and Skinfolds and diagnose obesity. There may be a number of different reasons for the discordance in prevalence rates including the exclusion of subjects who had incomplete data or measurement characteristics intrinsic to DEXA that require different normative data. Future research should include subgroup analysis by gender and ethnicity, inclusion of the BIA data from NHANES 03-04 and use of hydrostatic weighing as a gold standard for comparison.
Poster 50
RAC1/RAC3 INTERACTION WITH SMGGDS-607 AND SMGGDS-558
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The small GTPase Rac1 is an emerging target for cancer and atherosclerosis because it regulates cellular proliferation and migration. Rac3 is a closely related small GTPase that differs from Rac1 in sequence only at a few amino acids. SmgGDS is a unique guanine nucleotide exchange factor that is expressed in both lung cancer and vascular smooth muscle cells. This project explores the hypothesis that Rac1 interacts with the splice variants of SmgGDS, and that this interaction is regulated by specific amino acids near the C-terminal of Rac1. Rac1’s interaction will also be compared with Rac3’s ability to bind SmgGDS. Rac1 and SmgGDS proteins were translated in vitro and their interaction was tested by immunoprecipitation of SmgGDS. We found that Rac1 strongly interacts with both splice variants of SmgGDS while Rac3 does not. Mutating the arginine to a proline at position 185 in Rac1 decreases its affinity to SmgGDS. Mutating the proline to an arginine at position 185 in Rac3 increases its affinity to SmgGDS. Mutating the lysine to a glycine at position 186 in Rac1 more drastically reduces Rac1’s interaction with SmgGDS. However, mutation of both amino acids at positions 185 and 186 simultaneously slightly rescues Rac1’s ability to interact with SmgGDS. The amino acids in the C-terminal region of Rac1 and Rac3 have a complex role in regulating the interaction of both Rac proteins with SmgGDS. Future immunoprecipitation experiments can be conducted with different Rac1 and Rac3 C-terminal mutations to thoroughly examine the complexity of this binding.

Poster 51
MITOCHONDRIAL-GENERATED ROS, THROUGH ACTIVATION OF THE STRESS RESPONSE PATHWAY, DOWNREGULATES THE INSULIN SIGNALING PATHWAY.
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Increased oxidative stress has been linked to the development of insulin resistance and its progression to diabetes. Studies in skeletal muscle and adipose cells have proposed a role for reactive oxygen species (ROS) in impairing the insulin signaling pathway. However, the exact mechanism by which ROS lead to the impairment of insulin signaling is not well understood. Furthermore, cellular mechanisms for the hepatic insulin resistance are poorly understood. Studies have shown increased basal activation of the stress-signaling kinases p38 mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK) in obese and/or diabetic subjects, while other studies show the association between oxidative stress and the activation of the stress-response pathway. Therefore we hypothesize that mitochondrial-generated ROS stimulate crosstalk between the insulin signaling pathway, and the stress-response pathway. Our research focuses on primary rat and mouse hepatocytes to demonstrate whether (1) ROS production from the mitochondrial electron transport chain complexes inactivates the insulin signaling pathway; (2) p38 MAPK and JNK stress-signaling pathways are involved in the mechanism of ROS-induced impairment of the insulin signaling pathway. Young C57BL/6 mice are used for liver perfusion and the primary hepatocytes are treated with insulin or rotenone, a mitochondrial-ETC complex I inhibitor, or with a combined treatment; cells are harvested and the cytoplasmic proteins are subjected to western blot analysis and immunoprecipitation techniques. Our preliminary data show (a) that the IRS-1 is phosphorylated at the Ser307 with Rotenone treatment, indicating inactivation of the insulin pathway; (b) that P-Thr183/Tyr185JNK, as well as p38 MAPK bind to the IRS-1 upon activation by Rotenone treatment, suggesting that the ROS-inactivation of the IRS-1 involves JNK and p38 MAPK; and (c) that MKK4, as well as MKK3/6, upstream kinases, bind to the IRS-1 upon activation by Rotenone treatment. We conclude that the insulin and the stress signaling pathways crosstalk and that the mitochondrial-generated oxidative stress downregulates the insulin signaling pathway in the liver through its effect on the stress signaling proteins. Future studies will use specific inhibitors of JNK and p38 MAPK to confirm the role of these stress proteins in the inactivation of the insulin signaling.
Poster 52

8-OXOGUANINE AS THE POSSIBLE CAUSE OF CELLULAR SENESCENCE

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8-oxoguanine (8-oxoG) is a widely studied oxidative lesion implicated in mutagenesis and carcinogenesis through the generation of G:C:C:G and G:C:T:T. A transversions while remaining in the DNA. It is removed from the DNA primarily by DNA glycosylases involved in base excision repair, the most important being 8-oxoguanine DNA glycosylase 1 (OGG1). Our project evaluates the biological response to free 8-oxoG released through repair. We provide convincing evidences that link free 8-oxoG to premature senescence. This phenomenon occurs via 8-oxoG-induced increases in cellular levels of reactive oxygen species (ROS) and effects on receptor independent cell activation signaling via small GTPases, including Ras and Rac. 8-oxoG-induced senescence features natural senescence morphology, increased expression of β-galactosidase, and accumulation of lipofuscin granules. The cell cycle arrest is initiated and maintained by the tumor suppressors p53 and pRb and the cyclin-dependent kinase inhibitors p16 and p21. The observed senescence is not associated with accelerated telomere shortening, increased mutation rate, or increased levels of double strand breaks. The free 8-oxoG-mediated Ras activation and subsequent MEK/ERK phosphorylation is initially mitogenic, but its unscheduled activation results in cell stress and initiation of cell cycle arrest. Among the damaged and intact nucleosides and nucleoside bases, only 8-oxoG was capable of inducing premature senescence, significantly elevating cellular ROS levels, and activating small GTPases. Although it requires further investigation, our data show that 8-oxoG is a functional signaling molecule that could be a master regulator of natural senescence and aging processes.

Poster 53

HNRNP-U’s INTERACTION WITH NEIL1 AND ITS ROLE IN NEIL1 INITIATED BASE EXCISION REPAIR

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In aerobic cells, reactive oxygen species (ROS) including free radicals are the most frequent source of DNA damage. NEIL1 is a member of the NEIL family of DNA glycosylases that have been shown to initiate repair of endogenous and induced oxidized bases in the genome via the DNA base excision repair (BER) pathway. Unlike other mammalian DNA glycosylases, NEIL1 preferentially repairs base lesions on single stranded DNA regions, suggesting preferential activity during DNA replication and/or transcription. HnRNP-U is a major structural component of RNA binding complexes and is the largest member of the HnRNP family of RNA binding proteins. HnRNP-U, also known as scaffold attachment factor 1 (SAF1) has several proposed functions in RNA processing and is also involved in DNA mediated processes including chromosomal organization, transcriptional regulation and DNA replication. Our long-term goals are to characterize the dynamics and structural basis of the interaction between hnRNP-U and the enzymes of BER, including NEIL1, in order to unravel hnRNP-U’s role in BER. At present, we have identified hnRNP-U as one of the major proteins of the NEIL1-1-FLAG immunopulldown complex isolated from human cell extracts, and have confirmed physical interaction between the proteins using GST pulldown and Far Western analysis. We have mapped the region of protein-protein interaction to the disordered region near the C-terminus of NEIL1, a region which is dispensable for NEIL1’s DNA glycosylase activity. Interaction of hnRNP-U with NEIL1 takes place on its disordered regions near the N-terminus (residues 1-235) and the C-terminus (residues 651-806). Intrinsic fluorescence studies revealed that the two proteins bind with a strong affinity. Additionally, we have shown that hnRNP-U stimulates the activity of NEIL1 in vitro in excising 5-hydroxyuracil from DNA substrates mimicking replication intermediates. Analysis of kinetic parameters showed that hnRNP-U enhances NEIL1 binding to substrate and also stimulates NEIL1’s turnover. Currently, we are working to determine the role of hnRNP-U in NEIL1 mediated BER using shRNA-mediated hnRNP-U downregulation. Studying the properties and consequences of the interaction between NEIL1 and hnRNP-U will enhance our understanding of the regulation of NEIL1-mediated DNA repair and the cellular response to oxidative stress.
BIREFRINGENCE BANDS IN ROD PHOTORECEPTORS ORIGINATE FROM DIURNAL VARIATION IN RHODOPSIN PACKING INTO OUTER SEGMENT DISC MEMBRANES
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Rod and cone photoreceptors are modified cilia specialized for light detection in vision. Photoreceptors have sophisticated transport machinery which is the origin of several types of retinal degenerations if it is disturbed. Understanding elements involved in photoreceptors transport machinery is the key to comprehend retinal degeneration and blindness in human. To learn more about photoreceptors biosynthesis we focus on rhodopsin synthesis and transport during light/dark cycles to recognize the origin of birefringence banding pattern originally described by Kaplan. Plasmids containing rod photoreceptor specific promoters driving the expression of rhodopsin fused to EGFP were constructed and used to make transgenic tadpoles. Transgenic frogs were maintained in a normal 12 hr light, 12 hr dark cycle prior to experiment upon which the durations of the light/dark cycles were altered for several weeks. The expression profiles of the transgene in outer segment compartments were then recorded from retinal explants using live cell confocal microscopy. Rhodopsin-EGFP fluorescence appeared in a striped pattern perpendicular to and along the length of the rod outer segment. Animals raised in a 12/12 light/dark cycle generated a pattern that was in phase with the birefringence banding pattern. Rearing animals in complete darkness or with continuous light resulted in more uniform appearance of the fluorescence and in disappearance of the birefringence banding. It appears that discs made in the dark phase possess higher fluorescence density compared to those made in light phase. RTPCR examination of the message levels of the rhodopsin showed no variation with dark/light phase. Exchanging the Xenopus opsin promoter with promoters for transducin alpha or arrestin did not alter the banding pattern of rhodopsin-EGFP; however, other peripheral or intrinsic membrane proteins tagged with EGFP did not show the banding pattern. We conclude that the birefringence banding phenomenon originates from diurnal variation in rhodopsin packing density in photoreceptor discs. The diurnal variation does not appear to be caused by variation in transcription, but could arise at any of a number of steps between (and including) translation efficiency, trafficking of rhodopsin to the site of disc synthesis and disc synthesis itself. Important issues to be addressed in the future are the magnitude of the variation and the impact the variation may have on rhodopsin signaling.

DEPROTONATION OF DOCOSAHEXAENOIC ACID IS RESPONSIBLE FOR A HYPERPOLARIZING SHIFT OF PRESTIN-ASSOCIATED CHARGE MOVEMENT
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Background: Docosahexaenoic acid (DHA) is an -3polyunsaturated fatty acid that modulates the function of a variety of membrane proteins including ion channels and rhodopsin. It is an essential fatty acid that is enriched in fish oils and often credited in improving cardiac health and being protective against several neurological pathologies, but its role in hearing is unknown. We have shown that increasing either cholesterol or DHA in the membrane of prestin-expressing human embryonic kidney (HEK) 293 cells results in a hyperpolarizing shift in the voltage at peak capacitance. Cholesterol is uncharged and is thought to mechanically modulate the function of membrane proteins. At physiological pH, the hydroxyl group in the hydrophilic head region of DHA is deprotonated.

Objective: The purpose of this study is to investigate whether the DHA induced voltage shift is dependent on its negative charge. Methods: Prestin-expressing HEK 293 cells were incubated with either DHA or methylated DHA, an esterified version of DHA wherein the proton of the hydroxyl group is substituted by a methyl group. Cells were visualized under 400x magnification and single, non-round isolated HEK cells displaying robust GFP fluorescence were selected. Cell membrane capacitance was measured with the patch-clamp technique in the whole-cell mode during a DC voltage ramp. Results: Measures of prestin-associated charge movement demonstrated a significant hyperpolarizing shift in the voltage at peak capacitance when incubated in DHA (-82 mV). There was no change in the presence of methylated DHA (-76 mV) as compared to untreated, prestin-expressing HEK cells (-75 mV), nor was there any measurable nonlinear capacitance in the absence of prestin, regardless of incubation media.

Conclusions: Our results demonstrate that deprotonation is required for DHA to modulate prestin-membrane interactions, indicating a lipoelectric effect, which contrasts with the lipomechanic effects of cholesterol. Future studies will involve using higher concentrations of DHA (up to 200 micromolar) to establish a dose-response curve to determine if the shift in the voltage at peak capacitance is a function of concentration.
Background: Trauma is the leading cause of death for individuals less than forty-four years of age. Following trauma, multiple organ failure continues to be the leading cause of morbidity and mortality. Previous research has shown, both clinically and in the laboratory, that glutamine possesses gut protective effects under conditions of hypoperfusion. This protection is mediated by an increase in the anti-inflammatory transcriptional regulator, peroxisome proliferator-activated receptor-gamma (PPAR.). It has been demonstrated that glutamine activates PPAR via an indirect ligand-dependent mechanism. 15-deoxy-.12,14-prostaglandin J2 (15d-PGJ2), a product of arachidonic acid metabolism, is the most potent natural, endogenous ligand identified for PPAR. Therefore, we hypothesized that 15d-PGJ2 is the ligand mediating glutamine-induced activation of PPAR. Methods: Intestinal epithelial cells were pretreated with increasing concentrations of glutamine (0 – 10 mM), and then cell lysates were analyzed by ELISA for 15d-PGJ2 concentration. The upstream mediators of arachidonic acid metabolism, COX-1 and COX-2, were measured by Western Blot. The products of glutamine metabolism, glutamate and glutathione, were analyzed by EMSA to investigate the level of PPAR. activity. Lastly, potential ligands of PPAR., which are derived from the lipoxygenase (LOX) pathway, were screened by liquid chromatography/tandem mass spectroscopy (LC/MS/MS). Results: We have demonstrated in the laboratory and clinically that glutamine administration to the post-ischemic gut is protective via activation of PPAR. In this study, the results demonstrate an inverse correlation between 15d-PGJ2 and glutamine concentrations and no change in the enzyme expression levels of COX-1 or COX-2. Similarly, there was no change in PPAR. activity by glutamate or glutathione concentrations as a function of glutamine. Preliminary results from LC/MS/MS suggest that concentrations of 15-HETE, 13-HODE and 13-OXO of the LOX pathway increase with increasing glutamine concentration. Conclusion: Though glutamine activates PPAR. by an indirect ligand dependent mechanism, the actual ligand remains unclear. It was demonstrated that glutamine does not activate PPAR. via 15d-PGJ2. However, preliminary data suggests that 15-HETE, 13-HODE and 13-OXO are all likely ligands. These LOX pathway products will be further investigated to determine their potential role in gut protection via PPAR. activation.

Poster 57
CHROMATIN LOOPING BETWEEN AN INTRONIC ENHANCER AND DISTAL PROMOTER REGIONS REGULATES HUMAN HEME OXYGENASE-1 GENE
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Heme oxygenase (HO) is the rate-limiting enzyme for degradation of heme, resulting in the formation of iron, carbon monoxide, and biliverdin. HO-1 has antioxidant, antiapoptotic, and anti-inflammatory properties and has potent cytoprotective effects in acute kidney injury. Previous studies have identified an intronic enhancer that requires regions in the HO-1 promoter for maximal stimulus-dependent expression, since mutations in distal promoter elements abolished enhancer activity. To test the hypothesis, that chromatin looping brings the enhancer in close proximity to the promoter regions, we performed the Capturing chromosome conformation (3C) assay in human proximal tubular epithelial cells (HK-2). Confluent HK-2 cells were treated with vehicle (DMSO) or hemin (5µM) for 2h, and crosslinked with formaldehyde to generate DNA-protein and protein-protein crosslinks. Cells were lysed, subjected to SDS to uncross-linked proteins and chromatin then digested with restriction enzyme (Bgl II). Cleaved fragments were ligated at low concentration and crosslinking efficiency was measured by quantitative real-time PCR. The results demonstrate that a hypersensitive site (HS-2) in the -4.5kb promoter region is in close proximity to the 220-bp enhancer region in intron 1, following hemin stimulation and not in vehicle treated cells. Restriction digestion with ApaL1 which cleaves the 220bp enhancer, leads to a loss of this stimulus-dependent chromatin looping. ChiP-Loop assay revealed that at least transcription factors, Sp1, JunB, and USF-1 are involved in the process of chromatin loop formation for the interaction between HS-2 and the 220-bp enhancer upon induction of HO-1 by hemin. These results indicate that hemin stimulation induces chromatin looping which brings the HS-2 promoter region in close proximity to the intronic enhancer and provide novel molecular insights into the architecture of the human HO-1 gene in renal epithelial cells.
Poster 58
TGF-β1 INHIBITS LYMPHATIC REGENERATION BY DIRECTLY INHIBITING LYMPHATIC ENDOTHELIAL CELL PROLIFERATION, DIFFERENTIATION AND INTEGRIN EXPRESSION, LEADING TO CLINICAL LYMPHEDEMA IN A MURINE SURGICAL MODEL

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Background: TGF-β1 negatively regulates tissue fibrosis/scarring and lymphatic repair during wound healing by an unknown mechanism. Integrins vital to cell proliferation and migration in endothelial cells and fibroblasts may be implicated in TGF-β1 knockdowkn of lymphatics. Objective: These experiments: 1) evaluated the role of TGF-β1 on wound repair and lymphatic regeneration following surgical lymphatic ablation, and 2) assessed changes in integrin expression by LECs in mediating TGF-β1 inhibition of lymphatic repair. Methods: In vivo, circumferential skin excisions and ligation of lymphatics were performed in mouse tails. Wounds were randomized with either collagen gel, collagen gel with TGF-β1, collagen gel with a TGF-β1 dominant negative virus, or collagen gel with LacZ adenovirus. Lymphatic regeneration was evaluated with tail volume measurements, lymphoscintigraphy and immunohistochemistry. In vitro, human LECs were exposed to graded doses of TGF-β1 either on fibronectin (FN) or on plastic. Cellular proliferation, tube formation, integrin expression and markers of lymphatic differentiation were assessed. Results: Compared to controls, at all time points the addition of TGF-β1 caused: 1) a 40% larger increase in tail volumes at 6 weeks post-operatively (p<0.03); 2) impaired lymphatic transport (p<0.001); 3) decreased LEC proliferation (p=0.007); 4) impaired lymphatic capillary regeneration; and 5) lymphatic fibrosis. Blockade of TGF-β1 by a dominant-negative virus resulted in a smaller increase in tail volumes from baseline (p=0.03), improved lymphatic transport (p<0.01), and increased LEC proliferation. TGF-β1 significantly inhibited LEC proliferation in a dose-dependent manner. Tubule formation in Matrigel and expression of LEC-specific markers were inhibited. TGF-β1 modulated the expression of both pro- and anti-proliferative integrins. Binding of alpha5 integrin by fibronectin altered the response of LECs to TGF-β1. Conclusions: TGF-β1 inhibits lymphatic regeneration following surgical wounding. Exogenous TGF-α1 impaired LEC proliferation and tubule formation and caused lymphatic capillary fibrosis, while blockade of TGF-α1 activity accelerated lymphatic regeneration. TGF-α1 causes LECs to de-differentiate and potently regulates pro- and anti-proliferative integrin expression. These findings suggest that TGF-α1 inhibition may improve lymphatic regeneration clinically, thereby reducing the risk of lymphedema.

Poster 59
A ROBUST, RELIABLE, AND FAST ASSAY TO IDENTIFY SMALL MOLECULES ENHANCING NUCLEAR FACTOR KAPPA B EXPRESSION IN HUMAN NEUROBLASTOMA CELLS.

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Tumor Necrosis Factor-a-mediated (TNF-α) nuclear factor kappa B (NF-κB) activation has been shown to protect neurons from excitotoxicity and β-amyloid. Also, NF-κB immunoreactivity in amyloid plaques from Alzheimer's patients is reduced as compared with their age-matched controls. Overexpression of IκB-α, the inhibitor of NF-κB, sensitizes neurons to excitotoxic insults. TNF-α directly and indirectly has been involved in the acquisition of Long Term Potentiation (LTP) and Long Term Depression (LTD), respectively, via the activation of NF-κB. LTP and LTD are cellular correlates of learning and memory, both highly impaired in Alzheimer's patients. Given this interesting background, we have embarked on a campaign to identify small molecules able to activate NF-κB, hypothesizing that they could affect both neurodegeneration and deterioration of learning and memory. We have developed, validated, and used a robust cell-based high throughput screening assay to identify small molecules that up-regulate NF-κB expression in human neuroblastoma cells. Our original cell-based assay uses a human neuroblastoma cell line, SH-SY5Y, stably transfected with an expression vector containing a part of the NF-κB promoter driving the firefly luciferase gene expression. The stable cell line responded to TNF-α exposure with a large increase of luciferase activity. Next, the assay was validated in robotic liquid handling platform and miniaturized to 1536 plate format. We consistently obtained a Z value above 0.7, thus indicating the robustness and high reproducibility of the assay. We have screened a total of ~320,000 small molecules and identified more than 1944 statistically significant compounds that have increased luciferase expression. 94% of these hits have been confirmed in concentration response experiments. Cluster analysis of the hits revealed 16 highly enriched chemical classes, and several powerful single compounds. We are proceeding with compound validation, which will include the evaluation of NF-κB induction levels, NF-κB activation by its relocation to the cell nucleus, their effects on neuronal physiology in rat primary cortical neurons, as well as in in vitro models of neurotoxicity. Using these novel compounds, we expect to generate insight into the role of NF-κB signaling in in vitro Alzheimer's disease models.
Insulin-like Growth Factor-I Receptor (IGF-IR) is a receptor tyrosine kinase that binds IGF-I and IGF-II and mediates the mitogenic and anti-apoptotic effects induced by the binding of these ligands. IGF-IR has been implicated in a number of human tumors including breast cancer. Data from human breast tumors has demonstrated that IGF-IR is over-expressed and potentially hyper-phosphorylated in breast cancer. In transgenic mouse models which over-express ligand dependent IGF-IR and a constitutively active ligand independent form of IGF-IR, respectively, both developed mammary hyperplasia and palpable tumors and some of the animals also showed evidence of metastatic lesions on their lungs. The specific gene targets of the IGF-IR signaling pathway and the role of these genes in the development and propagation of the tumors in the transgenic mice and further, breast cancer in humans is not known. Data compiled from microarrays performed in our lab on MCF7, MDA-MB 231, T47D breast cancer cells as well as MCF10A immortalized mammary epithelial cells, revealed a list of candidate genes which appeared to either be induced or repressed in the presence of IGF-I stimulation. The aforementioned cell lines were treated with either serum-free medium or serum-free medium plus IGF-I for 3 hours and 24 hours. The experiment was performed in biological triplicate and RNA was isolated at the two time points and used to perform the microarray. Data from the microarray revealed 3673 and 3727 genes that were regulated by IGF-I treatment in MCF7 and MCF10A, respectively, at 3 hours. Microarray data for MDA-MB 231 and T47D revealed a significantly lower amount of genes regulated by IGF-I treatment. Analysis of the data compiled from the microarray is now underway to identify particular genes of interest, and these genes will then be validated via qPCR, followed by functional studies to elucidate a biological mechanism of IGF-IR regulation of the validated genes and the role that these genes play in initiating or promoting breast tumorigenesis.

Poster 61
ROLE OF HEME OXYGENASE-1 IN CISPLATIN-MEDIATED AUTOPHAGY IN KIDNEY EPITHELIAL CELLS
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Cisplatin is a commonly used chemotherapy agent that accumulates mainly in the proximal tubule cells (PTC) of the kidney and causes dose-dependent nephrotoxicity. Cisplatin also induces autophagy in PTC. HO-1 (Heme Oxygenase-1) is also induced in PTC following cisplatin treatment and is cytoprotective in cisplatin nephrotoxicity. HO-1 is an anti-oxidant enzyme that catalyzes the breakdown of heme to equimolar quantities of iron, carbon monoxide and biliverdin. HO-1-/- mice have severe renal injury following cisplatin treatment compared to HO-1+/+ mice. The purpose of this study was to determine if HO-1 modulates cisplatin-induced autophagy. We generated primary PTC from HO-1+/+ and HO-1-/- mice and treated cells with cisplatin and analyzed changes in autophagy markers such as Beclin1, ATG5 and LC3-II. We also performed in vivo studies where mice were administered cisplatin and analyzed for apoptosis and autophagy at various time points. We generated an inducible HEK293 stable cell line that overexpresses HO-1 and tested these cells in cisplatin induced autophagy. In vitro, we show that HO-1-/- PTC have high basal levels of autophagy compared to HO-1+/+ PTC. Also, HO-1+/+ cells respond to cisplatin with an increase in autophagy. However, HO-1-/- cells do not show an increase in autophagy. HO-1 overexpressing HEK293 cells are more resistant to cisplatin induced cell death compared to cells not overexpressing HO-1. This resistance is accompanied with a partial inhibition in cisplatin-induced autophagy. In vivo, we induced nephrotoxicity by administering cisplatin to HO-1+/+ and HO-1-/- mice and observed an increase in autophagic vacuoles. Also, saline injected HO-1-/ control animals have a substantial number of autophagic vacuoles compared to HO-1+/+ mice. Although autophagy is conceived to be cytoprotective, it may not be so. As seen here, even in the presence of high basal autophagy, HO-1-/- cells are not protected from cisplatin induced cell death. Also, cells that overexpress HO-1 inhibit autophagy and are more resistant to cisplatin induced cell-death. This indicates that autophagy could be detrimental based on the cell environment. We believe that HO-1-/- are more susceptible to injury due to increased accumulation of heme. The decrease in autophagy in HO-1 overexpressing cells could be due to degradation of heme. Our future studies will be focused on the mechanism by which HO-1 modulates autophagy in cisplatin nephrotoxicity.
**Poster 62**

**ASSOCIATION OF HOMOZYGOUS HIGH-RISK ALLELES IN COMPLEMENT FACTOR H AND ARMS2 WITH DRUSEN STAGING OF AGE-RELATED MACULAR DEGENERATION (AMD)**

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**Background:** Elucidating the roles of complement factor H (CFH) Y402H and LOC287715/ARMS2 in the pathogenesis of age-related macular degeneration (AMD) can assist in optimizing treatment for patients in the future. **Objective:** To determine the association of homozygous high-risk and protective alleles in both CFH and ARMS2 loci, along with other risk factors, with the staging of AMD. **Methods:** 629 patients enrolled in the Macular Genetics Study classified with early or late stage AMD underwent genotyping to determine CFH and ARMS2 status. History of smoking, hypertension and sun exposure was obtained through questionnaires. From the initial set, 208 patients homozygous for either CFH or ARMS 2 high-risk or protective alleles (a total of four subgroups) were chosen for further analysis. **Results:** Of the 208 patients, 46% were graded early AMD (eAMD) and 54% were graded late AMD, including choroidal neovascularization (CNV) and/or geographic atrophy (GA). In patients with eAMD, those with homozygous ARMS2 risk allele compared to homozygous protective allele were more likely to present with stage 3 AMD (indistinct soft drusen and pigmentary changes) versus stage 2A or 2B AMD (soft indistinct drusen or soft distinct drusen with pigmentary changes, respectively) (OR 3.9, 95% CI 1.2, 12; p=0.02), whereas those with homozygous CFH risk allele versus protective allele were not (OR 1.4, 95% CI 0.5, 3.6; p=0.5). In comparing eAMD to late AMD, patients homozygous for both CFH and ARMS2 risk alleles were most likely (OR 6.2, 95% CI 1.9, 20; p=0.02) to develop late AMD. Patients with hypertension were less likely to develop late AMD (OR 0.4, 95% CI 0.2, 1.01; p=0.051). Patients homozygous for ARMS2 risk allele versus protective allele had a lower mean age of presentation with AMD (75 years versus 80 years). CFH and ARMS2 genotypes were not significantly associated with a specific form (CNV vs. GA) of late stage disease. **Conclusions:** Patients homozygous for ARMS2 risk allele, but not those homozygous for CFH risk allele, were more likely to present with the high-risk stage 3 than lower risk stages 2A or 2B, consistent with ARMS2 conferring risk for late AMD. Homozygosity for both CFH and ARMS2 high-risk alleles conferred the greatest risk for late AMD, but the form of late disease was not influenced. Hypertension appeared protective, perhaps secondary to medication use. Patients with homozygous ARMS2 risk versus protective allele had earlier age of presentation with AMD.

**Poster 63**

**KIDNEY AND MUSCLE PHENOTYPES DUE TO HYPOSIALYLATION IN A MOUSE MODEL OF HEREDITARY INCLUSION BODY MYOPATHY**

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Hereditary Inclusion Body Myopathy (HIBM) is a recessive adult-onset neuromuscular disorder, characterized by progressive muscle weakness due to mutations in UDP-GlcNAc 2-epimerase/ManNAc kinase (GNE), the key enzyme in sialic acid (SA) synthesis. We created a Gne knock-in mouse model harboring the human M712T mutation. We previously showed that these mice died before postnatal day 3 (P3) of glomerular disease, involving effacement of podocytes due to hyposialylation. Administration of the SA precursor ManNAc partially rescued the kidney phenotype and allowed survival of mutant mice. Here we evaluate SA itself as a therapeutic agent, by oral administration to pregnant and nursing mice. However, SA feeding did not significantly increase the number of surviving mice beyond P3. This is likely due to the negative charge of SA (impairing transmembrane transport) compared to the neutral charge of ManNAc. We also evaluated the evidence of a muscle phenotype in older surviving mutant mice. Electron microscopy studies of the gastrocnemius, gluteus, and quadriceps muscles of 6 and 11 month old mutant mice showed tubular aggregates (TAs). TAs presumably originate from the sarcoplasmic reticulum, and may be precursors of the rimmed vacuoles (RVs) seen in the muscles of HIBM patients, who are diagnosed late, after RVs have already formed. Further analysis of TA formation and sialylation status of affected muscles is being pursued, as well as evaluation of the effect of ManNAc on their formation. Other human muscular disorders characterized by TAs, including sporadic limb girdle weakness, familial myasthenia gravis, and unexplained exercise-induced muscle cramps, may be caused by local sialic acid deficiency. Our Gne M712T mouse is a good model for further evaluation of these hypotheses. In sum, our Gne M712T mouse unexpectedly serves as the first genetic model of podocyte injury due to hyposialylation, and may also prove to be a model of the myopathy of HIBM.
Background: In the nervous system, neurons and their precursor cells are formed in different regions but migrate and occupy very specific positions in the mature CNS. Elucidating the mechanisms that govern the initiation, maintenance, and the termination is crucial for our understanding of how a functional neuronal circuitry is established in the nervous system during neurogenesis. Objective: To identify the genes and the underlying signaling pathways involved in neuronal migration in the nerve system by using Drosophila as a model system. Methods: All crosses were performed at 25C unless otherwise indicated. For confocal microscopy of embryos, cy5 and FITC-conjugated secondary antibodies were used. For light microscopy, alkaline phosphatase or DAB-conjugated secondary antibodies were used. Results: A neuronal migration defect was identified in the Drosophila ventral nerve cord (VNC) in the Hem protein (Hem) mutant, Hem[j4-48]. NB4-2.GMC-1.RP2/Sib is one of the most typical and well-studied cell lineages in Drosophila VNC. In Hem[j4-48], RP2 neurons crossed the midline and migrated from their initial hemisegments, to the other hemisegments; however, Sib cells remained still, which indicated that this migration defect was RP2 specific. This migration defect was not caused by midline defect, cell identity change or VNC distortion. Disruption of parasegmental boundary could eliminate this abnormal migration pattern. A mini-screen showed that loss of function of abl displayed the similar migration defect. Conclusions: Our results showed that Hem protein was involved in the regulation of neuronal migration in the Drosophila VNC. Loss of function of Hem altered the normal migration pattern of RP2/Sib cell lineage, which could be due to disrupted interaction between Hem protein and the parasegmental boundary. Abl, a cytoskeleton organization protein, retrieved in a mini-screen displayed the same abnormal migration pattern in the mutant of loss of function. As a result, was also considered to be involved in the signaling pathway of neuronal migration. Future studies will focus on 1) screening for more genes involved in the signaling pathway of neuronal migration and exploring the underlying mechanisms, 2) revealing the interactions between Hem and parasegment boundary during the neuronal migration in the development of the Drosophila ventral nerve cord.

Poster 65
DLX Transcriptional Regulation of Insulin Expression during Pancreatic Development
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Insulin is important for the regulation of glucose homeostasis and diseases such as Diabetes Mellitus result when insulin signaling is impaired. The insulin gene is highly regulated by transcription factors including PAX6 and NeuroD1. We hypothesized that: (i) DLX2, a homeobox transcription factor, directly up-regulates insulin transcription in the developing pancreas. (ii) Dlx1/2 mutations result in abnormal pancreatic islet development. (iii) DLX2 interacts with PAX6 in regulating Insulin transcription. Methods: 1) Immunofluorescence (IF) of E18.5 mouse pancreas used DLX2, Insulin, PAX6 and NeuroD1 antibodies. 2) Chromatin immunoprecipitation (ChIP) used embryonic striatum and hindbrain. 3) Reporter gene assays used sequence confirmed PCR products of the preproinsulin-I promoter region isolated by ChIP subcloned into a luciferase reporter vector and co-transfected with DLX2 into HEK 293 and ßTC cells. 4) ELISA of serum and pancreas from wild-type (wt) and mutants. 5) Co-immunoprecipitation (co-IP) assays using embryonic tissues. Results: 1)IF: Pancreatic islets cells co-expressed DLX2 and Insulin and co-localized DLX2 with PAX6 and NeuroD1. Insulin expression was decreased in Dlx1/2 mutant pancreas. 2) ChIP assays: DLX2 bound to four regions of the preproinsulin-I promoter region isolated by ChIP subcloned into a luciferase reporter vector and co-transfected with DLX2 into HEK 293 and ßTC cells. 4) ELISA of serum and pancreas from wild-type (wt) and mutants. 5) Co-immunoprecipitation (co-IP) assays using embryonic tissues. Results: 1)IF: Pancreatic islets cells co-expressed DLX2 and Insulin and co-localized DLX2 with PAX6 and NeuroD1. Insulin expression was decreased in Dlx1/2 mutant pancreas. 2) ChIP assays: DLX2 bound to four regions of the preproinsulin-I promoter and two regions of preproinsulin-II promoter 3) Reporter Gene Assays: Co-expression of Dlx2 resulted in the transcriptional activation of preproinsulin-I promoter expression in vitro. 4) ELISA: There was a 2.9 fold relative reduction of serum insulin levels in mutant mice. 5) Co-IP: PAX6-DLX2 complexes were demonstrated in embryonic pancreas and striatum. Conclusions: 1)DLX2 is co-expressed with Insulin and key regulatory proteins PAX6 and NeuroD1 in ß-cells in vivo. 2) DLX2 binds to regulatory regions of preproinsulin I and preproinsulin II promoter regions in vivo. 3) DLX2 activates preproinsulin-I promoter in vitro. 4) Dlx1/Dlx2 mutant mice have reduced insulin than controls. 5) DLX2 and PAX6 form protein-protein complexes in vivo. Thus DLX2 plays a major role in transcriptional activation of the preproinsulin-I gene. Future Directions: 1)Determine whether gain of Dlx2 expression is sufficient to increase expression of preproinsulin-I in islet explants. 2) Use interfering RNA strategies to knock down Dlx expression in islet explants. 3) Confirm that DLX2 directly and specifically binds to the preproinsulin promoter. 4) Determine sites of interaction between PAX6 and DLX2 proteins.
Mammalian development is a poorly understood process where rapid lineage decisions occur via the rapid regulation of crucial developmental genes. Given the rapidity by which development occurs, understanding how such genes are regulated is fundamental to understanding development. The aim of this study is to determine the mechanism(s) of activation of a developmental gene, Sox21, which is rapidly activated when ES cells differentiate. Many such developmental genes are targeted by the Polycomb Repressive Complex (PRC) which maintains repressive chromatin and prevents gene activation. PRC target genes often display activating (Histone3lysine4-H3K4 trimethylation) and repressive (Histone3lysine27-H3K27 trimethylation) histone modifications and are termed poised/bivalent genes. Importantly, in ES cells many poised genes are also occupied by master regulator transcription factors Sox2 and Oct4. They regulate a critical gene network by cooperatively binding to gene regulatory regions that contain adjacent HMG and POU motifs (HMG/POU cassettes). Based on these preliminary data, we hypothesize that the inactivity of poised genes, like Sox21, which are bound by Sox2 and Oct4 in undifferentiated ES cells, is due to its repression by PRC. Upon differentiation, PRC exits from these genes, enabling their rapid activation by Sox2 and Oct4. Recently, we developed a novel model system of ES cell differentiation, which we believe is uniquely suited to understanding how poised genes, like Sox21, are activated rapidly. We engineered mouse ES cells to inducibly overexpress Sox2. Importantly, this causes ES cells to differentiate into multiple lineages. Moreover, Sox21 a neural lineage marker is massively up regulated. We demonstrated by chromatin immunoprecipitation (ChIP) that Sox2 and Oct4 are associated with a putative HMG/POU cassette of the Sox21 gene before and after the induction of differentiation. We also found that the marks of bivalency at the Sox21 gene are resolved during differentiation. ChIP analysis revealed that the Sox21 gene is occupied by PRC component Suz12, and H3K27 and H3K4 trimethylation before differentiation. Upon the induction of differentiation both Suz12 and H3K27 trimethylation are lost from the Sox21 gene, while H3K4 trimethylation and RNA Polymerase II are retained. These studies support our conclusion that a poised gene like Sox21 experiences rapid changes in histone modifications, which favor its rapid activation when ES cells differentiate.

Poster 67
IDENTIFICATION OF GENE MUTATIONS WITHIN FAMILIES WITH MONOGENIC DISEASE THROUGH LINKAGE ANALYSIS
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BACKGROUND: There are many families whose members present with a similar disease phenotype, which follows an autosomal dominant, recessive or X-linked inheritance pattern, suggesting a monogenic basis for the disease. Often, despite the inheritance patterns demonstrated, the molecular genetic diagnosis remains unidentified due to the lack of effective genetic tests available for diseases that are genetically heterogeneous. OBJECTIVE: To use linkage analysis to identify gene mutations in 13 families with various monogenic disease, such as thrombocytopenia, Waardenburg Syndrome and myopathy. METHODS: DNA was isolated from saliva or blood samples from 13 families with various monogenic disease phenotypes. We used 250K single nucleotide polymorphism (SNP) Affymetrix arrays to perform genotyping on all the family members. We then used linkage analysis tools, such as Plink, Merlin and dChip to perform parametric analysis. With these results, we identified chromosome regions linked to the disease in affected family members. We then used the human genome map to look for candidate genes within the established chromosome regions that may cause the disease phenotype. The coding and conserved regulatory sequences of the candidate genes were then sequenced and analyzed for mutations in the probands and other affected family members. RESULTS: Chromosome regions, which appeared to be linked to the disease phenotype, were established for 8 families with various monogenic diseases. LOD scores up to 2.07 were obtained, depending on the number of family members within the pedigree. Single nucleotide changes that did not result in altered amino acid sequence were identified within the candidate genes sequenced, but no mutations that would affect amino acid structure or promoter regions were identified. CONCLUSIONS: Despite the failure to identify gene mutations using this linkage-analysis approach, the high LOD scores demonstrating linkage suggest it is possible that another gene within the specified regions is mutated. Moreover, it is possible that the mutation is in a gene whose function has not been established to date. To determine the utility of linkage analysis for identifying gene mutations in single families, future studies must continue to identify and sequence candidate genes within the established regions with high LOD scores.
ADIPOSE TISSUE IS A MAJOR SOURCE OF IL-6 PRODUCTION AND CONTRIBUTES TO AGE-ASSOCIATED MORTALITY DURING SEPSIS
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Aging is characterized by a deteriorated stress response that underlies a compromised resistance to physiological stress. Sepsis, an infection-initiated systemic inflammatory response syndrome, is a serious problem as elderly patients with this condition suffer much higher mortality than younger patients. It is well known that upon challenge with bacterial endotoxin lipopolysaccharide (LPS), aged mice exhibit significantly higher mortality than younger mice, and this mortality is closely associated with augmented induction of pro-inflammatory cytokine interleukin-6 (IL-6). However, the major site of IL-6 over-expression is not entirely known. The objective of this study is to provide evidence that white adipose tissue is the major site of IL-6 production during LPS-induced systemic inflammation and to define the upstream mechanisms leading to age-associated differences in this cytokine.

Systemic inflammation was induced in young (4-7 months) and aged (18-27 months) C57BL/6 mice by intraperitoneal injection with LPS. Among the various tissues examined, white adipose tissue from the epididymal fat pad expressed the highest levels of IL-6 mRNA in both young and aged wild-type mice with a 5.5-fold higher level in the aged (p<0.001). Compared to age-matched wild-type mice, aged IL-6 -/- mice exhibited reduced mortality when injected with LPS (p<0.05) suggesting a deleterious effect of IL-6 over-expression in the aged. Immunohistochemistry revealed that within the adipose tissue, white adipocytes expressed the highest levels of IL-6 though vascular endothelial cells and inflammatory cells also contributed. Furthermore, adipose tissue reduction by dietary restriction lead to significant resistance to LPS-mediated systemic inflammation with a 10-fold decrease in circulating IL-6 levels (p<0.001). We further show that the age-dependent difference in IL-6 production by the adipose tissue can be reproduced in vitro through LPS treatment of adipose tissues in organ culture and that this difference may be a downstream effect of tumor necrosis factor alpha (TNF) induction in other tissues. Taken together, these results demonstrate that increased vulnerability to sepsis with age is due in part, to augmented IL-6 production by the adipose tissue.

DENDRITIC CELL MODULATION ENHANCES NEUTROPHIL-MEDIATED RESISTANCE TO BURN WOUND INFECTION
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Patients with severe burns are susceptible to life-threatening opportunistic infections due not only to loss of the skin as a protective barrier but also to numerous immunological alterations that are induced by burn injury. Resistance of mice to a burn wound infection can be significantly increased by prophylactic treatment with fms-like tyrosine kinase-3 ligand (Flt3L), a hemopoietic cytokine and dendritic cell growth factor, after severe burns. Flt3L treatments significantly increase dendritic cell numbers, but dendritic cells are not directly bactericidal. Neutrophils are not directly modulated by Flt3L, but can be activated by direct interactions with dendritic cells. The purpose of this study was to determine if neutrophils mediate the protective effects of Flt3L on survival after burn wound infection. To test this hypothesis, mice received a full-thickness scald burn to 35% of their surface area under deep anesthesia, followed by daily injections with Flt3L or Lactated Ringer's (LR; control) solution. Three days after injury, neutrophils were depleted by injection with an antibody specific for Ly6G+ neutrophils (clone 1A8), and wound were inoculated by topical application of Pseudomonas aeruginosa. Bacterial cultures were performed 16 hours later, and myeloperoxidase was assessed in dendritic cell-neutrophil co-cultures. Survival was also monitored. Neutralization of neutrophils abrogated the protective effects of Flt3L on survival and bacterial clearance. Additionally, dendritic cells from Flt3L-treated mice appear to enhance myeloperoxidase production by neutrophils in culture. These data indicate that neutrophils play a critical role in Flt3L-mediated resistance to burn wound infection.
Tuberculosis (TB) remains a global health problem with more than 8 million new cases and 1 million deaths per year worldwide. HIV-1 infected persons have a greatly increased risk of Mycobacterium tuberculosis (M. tb) co-infection. A key feature of M.tb infection is the formation of granulomas, cellular accumulations composed of macrophages, epithelial cells, and a surrounding mantle of T cells, which are important for the containment of infection. The cytolytic T cell effector molecules, perforin and granulysin, play a critical role in protective immunity to M.tb. It has been shown that decreased expression of perforin and granulysin at the site of pulmonary disease is linked to chronic TB. However, the effects of HIV-1 on CD8+ T cells numbers and expression of cytolytic effector molecules such as perforin and granulysin in M. tb induced granulomas has not been explored. In this study, we used immunohistological techniques to assess the differences in T cell populations, granulysin expression, and pathology in tissue sections from Mtb- and Mtb/HIV-1-infected human lung. Our results indicate that granulomas from persons with TB/HIV-1 are characterized by dysregulated T cell organization and poor expression of granulysin. We propose that defective granulysin expression by M.tb-specific CD8+T cells contributes to the development of disease in TB/HIV-1 co-infected persons.

Background – Both severe burn injury and obesity have been shown to elicit an abnormal inflammatory response. With a large percentage of the American population being obese, it has become increasingly important to understand the effects of the obesity on the post-burn-injury state. Objectives – Describe the pattern of temporal variance of leukocyte count after a severe burn injury. Analyze this response with respect to BMI, age, and incidence of infection. Determine if BMI status impacts leukocyte response. Methods – Data were obtained from the Trauma-Related Database of the Inflammation and the Host Response to Injury research program. Leukocyte counts were organized by time post-injury into 12 and 24-hour groups. The average age of patients included was 40.0 years. BMI was calculated and classified based on CDC age-appropriate definitions and grouped into NORM (18.5-24.9 kg·m^2), OVER (25-30 kg·m^2), and OBESE (>30 kg·m^2). Nosocomial infections were defined as bacterial or fungal infections not in burn wound area and also organized into 24-hour groups. Results – Leukocyte count: OVER and OBESE had a non-significant increase while NORM had a non-significant decline from first period (0-11 hr) to second period (12-23 hr). All groups declined after 12-23 hr and reached normal range by 72-95 hr. No groups became leukocytopenic. From the initial recorded peak to the lowest recorded values between hrs 48-95, there were characteristic reductions of 75.7, 75.5, and 80.1% in NORM, OVER, and OBESE respectively. At 144-167 hrs, NORM was greater than OVER, p=0.018. At 192-215 hrs, OVER was greater than NORM, p=0.013. At 384-407 hrs, NORM was greater than OVER, p=0.044. Nosocomial infections: There were no significant differences found between BMI groups at any time intervals. Conclusion – This analysis has shown that obesity does not produce consistent significant differences in leukocyte number following thermal injury. The suggestion of an initial differential response within the first 12 hr post injury may warrant that smaller intervals be studied. Future research may investigate the nature of the leukocytes present, given that cell number is only half of determining cell function.
Background: Theories regarding the pathogenesis of inflammatory bowel disease (IBD), ulcerative colitis (UC) in particular, suggest that the disease represents a disruption in gut tolerance to the intestinal microflora, leading to dysregulation of mucosal CD4+ T cell activity and chronic inflammation. One regulatory pathway of these responses involves PD-1/PD-L1 negative co-stimulator interactions between T cells and antigen presenting cells (APCs). It has been shown that human colonic myofibroblasts (CMFs) are novel non-professional APCs that express negative co-stimulators PD-L1/L2 and are capable of suppressing proliferation of activated CD4+ T cells. Most importantly, strong upregulation of PD-L1 was observed in CMFs isolated from UC patients when compared to normal colon. However, the mechanisms of PD-L1 expression in CMFs remain unknown. The aim of the project was to determine whether stimulation of toll-like receptor 4 (TLR4) with pathogen-associated molecular pattern (PAMPs) structures of bacteria can modify PD-L1 expression in CMFs.

Methods: PD-L1 expression in human CMFs in response to the bacterial stimuli in presence/absence of the agonists/inhibitors of TLR-4 and TLR5 signaling was quantified using real-time RT-PCR and flow cytometry analysis. Salmonella typhimurium was chosen as a model of bacterial PAMPs, possessing well-characterized TLR-4 and TLR-5 ligands (e.g. LPS and flagellin, respectively). Results: Stimulation of the CMFs with S. typhimurium resulted in a significant increase in PD-L1 expression. That PD-L1 upregulation involves TLR4 signaling, since it was significantly decreased in presence of the LPS inhibitor, polymixin B as well as with TLR 4 blocking antibodies. In contrast, there was only a slight decrease in PD-L1 upregulation when TLR 5 antagonist was added. Moreover, stimulation of CMFs with purified LPS (TLR-4 ligand) results in significant upregulation of PD-L1. Conclusion: Our data demonstrates that PD-L1 expression in CMFs can be upregulated via TLR4-dependent signals. These results support our hypothesis that CMFs may suppress the response of activated CD4+ T cells via expression of negative co-stimulator PD-L1. This data further suggests that TLR-4 may be one of the many mechanisms that contribute to PD-L1 over-expression in active UC.

Poster 73
ROLE OF REGULATORY T-CELLS IN B-CELL ANERGY AND AUTOANTIBODY PRODUCTION
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Background: B cells are vital for adaptive immunity, secreting antibodies that help eliminate foreign pathogens. However, some B cells are instead specific for our own body and are termed “auto-reactive”. Three mechanisms prevent auto-reactive B cells from mounting an immune response. One of these mechanisms, called anergy, prevents auto-reactive B cells in the peripheral immune system from becoming activated and from secreting auto-reactive antibodies. The mechanisms that regulate B cell anergy are not fully known but are vital if we are to understand the development of autoimmune diseases. Regulatory T cells (Tregs) are CD4+ lymphocytes expressing CD25 and the transcription factor FoxP3 and help regulate immune processes. Loss of Tregs in humans (a condition called IPEX) is a fatal disorder whose symptoms include severe autoimmunity. Objectives: Whether Tregs control auto-reactive B cells is unclear. We hypothesize that Tregs regulate B cell anergy, preventing these cells from contributing to autoimmunity. To test this hypothesis we first examined whether loss of Tregs cells alters total B cell development. Then secondly; whether the loss of Tregs specifically altered the development of anergic B cells and autoantibody production. Methods: We used a transgenic mouse model that fails to express the FoxP3 protein and consequently lacks Tregs. Flow-cytometry was used to examine the surface phenotype and presence of both normal B cells and the presence of a newly defined anergic B cell population called An1 cells. The development of autoimmune disease was determined using an enzyme-linked-immunosorbant-assay or HEP-2 cells to determine if anti-DNA/nuclear auto-antibodies were present in the serum of experimental mice. Results: We observed that loss of Tregs caused a drastic change in B cell development, including a loss of the anergic An1 B cells population. We also showed that loss of Tregs lead to the production of auto-antibodies. Adding Tregs back to our mice reversed both these observations. Conclusions: Loss of Tregs prevents the development or promotes the loss of anergic An1 B-cells. The results supported our hypothesis that Tregs may regulate autoreactive B cells thus controlling autoimmunity. These results are a step in exploring the etiology and mechanism of the human disease IPEX. In future studies, we will characterize the molecular mechanisms that explain our observations and define how Tregs regulate auto-reactive B cells.
GROWTH FACTOR RECEPTOR BOUND PROTEIN 2 (GRB2) IS A KEY FACTOR IN MEDIATING ENTRY OF ECOTROPIC RETROVIRUS.

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BACKGROUND: Cell entry is the first critical step for any virus to establish infection. Entry comprises the steps of receptor binding, internalization and for enveloped viruses, membrane fusion. It is known that cellular proteins are required in this process. For retroviruses, such as HIV-1 and ecotropic murine leukemia virus (MLV), active receptor recruitment and trafficking take place during viral entry, however, the underlying mechanisms are largely uncharacterized. OBJECTIVE: The objective of the study is to elucidate the interaction between cellular factor and virus receptor during retrovirus entry. METHODS: A siRNA screen was designed to detect cell gene products important for virus infection, we identified Grb2 (Growth factor receptor bound protein 2), as a key protein for infection by ecotropic MLV, a classical model for retrovirus infection mechanism and pathogenesis. Dominant negative Grb2 mutants that carry amino acid substitutions in different functional domains (Grb2-SH2m, Grb2-NCSH3m) were expressed in 293HEK cells that stably express virus receptor, mouse cationic amino acid transporter 1 (mCAT1), and subsequently, cells were assay for infectivity by FACS analysis. The effects of Grb2 on mCAT1 distribution and trafficking were observed by immunofluorescence labeling and confocal microscopy. A GST pull-down assay was employed to characterize the physical interaction between mCAT1 and Grb2 during MLV entry. RESULTS: FACS analysis revealed that only the expression of Grb2-SH2m significantly reduced MLV infectivity. The confocal microscopy study showed that expression of Grb2-SH2m resulted in sequestration of mCAT-1 into the cytoplasm, as opposed to its normal location on the plasma membrane. Additionally, we found a time-dependent increasing association of Grb2 and mCAT1 following incubation with MLV that correlated with MLV entry kinetics. CONCLUSIONS: Together, these findings suggest that Grb2 plays an important role in initiating infection by affecting the trafficking of viral receptor mCAT1. Further studies need to be done to identify the structural domains in mCAT1 to interact with the viral proteins, and to dissect the exact involvement of Grb2 during different stages in MLV entry.

THE EFFECTS OF TICK SALIVA ON THE DENDRITIC CELL-RICKETTSIA INTERACTION, IN VITRO

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Background: Spotted fever group rickettsioses are life-threatening emerging and re-emerging tick-borne infectious diseases. The severity of rickettsioses is hypothesized to be associated with host responses regulated by various immune cells. Dendritic cells (DCs) are early target cells during rickettsial infections. Since rickettsial transmission occurs via the skin following tick bite, we hypothesized that tick saliva plays an important role in the pathogenesis of rickettsial diseases through suppressing protective host immune responses. Here, we aimed to investigate the effects of tick saliva on interaction of DCs with Rickettsia conorii. Methods: Bone marrow derived DC (BMDC) were isolated from C3H/HeN and C57BL/6 mice, which are susceptible and resistant to R. conorii infection, respectively. R. conorii-infected BMDCs were exposed to saliva (60 µg/ml) from Rhipicephalus sanguineus sanguineus ticks, the natural vector of R. conorii. After 24 h incubation, supernatant was collected for measurement of cytokines, nitric oxide, and indoleamine 2, 3-dioxygenase production. The effects of tick saliva on DCs’ maturation were determined by measuring expression of multiple markers on R. conorii-infected DCs with or without exposure to tick saliva. Results: Tick saliva significantly enhanced the expression levels of MHC-II and the co-stimulatory molecule CD86 on R. conorii-infected DCs and CD80, and CD8. In contrast, expression levels of MHC class II, CD86 and MHC-I on DCs of C57BL/6 mice were unaltered. The expression levels of B220 and CD8 were increased in untreated R. conorii-infected DCs of both resistant and susceptible mice. However, tick saliva inhibited the expression of B220 on infected DCs of resistant C57BL/6 mice, implying decreased differentiation into plasmacytoid DCs potentially inhibiting the innate immune system of C57BL/6 mice during rickettsial infection. Conclusions: These results indicate that tick saliva could give an early advantage tick-borne pathogens. This study contributes substantially to understanding the role of the innate immune system in naturally occurring rickettsial infections and will be further studied using skin derived DC as well as in vivo studies.
PHYLOGENETIC ANALYSIS OF HIV-1 IN GALVESTON, TX
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Background: The genetic diversity of HIV is important clinically as personalized medicine is being targeted for the treatment and vaccine development is being studied for the prevention of HIV infection. Phylogenetic relationships have been made based on sequence homology allowing classification of HIV into types, groups, subtypes, and sub-subtypes. In addition, a circulating recombinant form (CRF), a mosaic virus formed from recombination during co- or super-infection, has also been recognized and further increases genetic diversity. The Abbott ViroSeq HIV-1 Genotyping System is FDA approved to genotype protease and reverse transcriptase of HIV-1 group M subtype B as this was the most prevalent strain when the assay was developed approximately ten years ago. However, epidemiology studies indicate previously thought less common strains in the USA have gained in prevalence. According to His-Hsun Lin et al (2006), genetic characterization of HIV-1 strains in an immigrant population in New York revealed non-B subtypes and CRFs accounted for 43.4% of 196 samples [1]. The response to medications by non-B subtypes compared to B subtypes, as well as whether homologous mutations in non-B subtypes contribute to drug resistance the same as B subtypes, have not been studied well. Objective: The purpose of this study is to identify whether HIV viruses routinely tested using the ViroSeq assay are subtype. Methods: Sequencing results generated routinely in UTMB Molecular Diagnostics Laboratory were run in the Stanford HIV database (http://dbpartners.stanford.edu/RegaSubtyping) in order to be subtyped. The sequences were then used to create a Maximum Likelihood phylogenetic tree using Phylip after aligning with ClustalX. Results and Conclusions: We analyzed 200 HIV sequences and identified co-/super- infection of subtype B with other subtypes and CRFs. A detailed analysis is ongoing in order to reach statistical significance.

EFFECTS OF SUBTHERAPEUTIC DOSAGES OF ANTIBIOTICS ON EARLY LIFE WEIGHT GAIN OF MICE
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Antibiotics have been widely used in the agricultural industry for over 50 years. When administered in subtherapeutic doses to healthy livestock and poultry, antibiotics provide a significant boost to weight gain and feed efficiency, termed “growth promotion,” but the mechanisms are unknown. We hypothesize that subtherapeutic antibiotic administration may alter the gut microbiome, potentially allowing more efficient nutrient uptake. To examine our hypothesis, we administered subtherapeutic doses of antibiotics to healthy C57BL/6J mice and monitored their growth. Mice were given standard chow and water ad libitum. Based on FDA-approved subtherapeutic dose guidelines, their drinking water contained vancomycin, penicillin, vancomycin + penicillin, or chlorotetracycline, or no antibiotic. Weight measurements and feed efficiency were monitored, and body composition was examined through DEXA analysis. Genetic variation of the colonic microbiome was examined using randomly amplified polymorphic DNA (RAPD) polymerase chain reaction (PCR). There were no statistically significant differences in overall growth measurements between the control and antibiotic-exposed groups. However, fat mass in antibiotic-exposed mice: vancomycin (4.23±0.54g), penicillin (4.77±1.00g), vancomycin + penicillin (4.63±0.70g), and chlorotetracycline (4.22±0.42g) was significantly (all p<0.05) increased compared to controls (3.88±0.17g). Percent body fat in the antibiotic-exposed mice [penicillin (24.17±3.51%), vancomycin + penicillin (23.75±3.23%), and chlorotetracycline (21.63±1.27%)] also were significantly (all p<0.05) increased compared to the control mice (20.17±1.40%). Gut microbiome analysis by RAPD PCR produced differing DNA profiles for control and penicillin-exposed mice, indicating sequence-level variation between the two study groups. We conclude that exposure to subtherapeutic antibiotics altered murine body composition, suggesting a mechanism related to changing gastrointestinal microbiota.
Dormant spores of bacteria of Bacillus species are potential vectors of food spoilage and disease. Therefore rapid detection of these organisms is extremely important. Currently, spore detection is by colony forming assays and while these assays are reliable, they are relatively slow. Hence other methods of detection have been proposed. One approach is the use of spore fluorescence, either fluorescence induced by binding of an appropriate dye or autofluorescence, a phenomenon exhibited by spores of many species, and subsequent detection of fluorescent spores by flow cytometry. The spore structures responsible for their autofluorescence and where fluorescent dyes bind is unknown. However, it is hypothesized to be due to the proteinaceous spore coat, the thick peptidoglycan cortex, or either of the two membranes between the coat and the cortex. There could be several potential benefits to determining the causes of spore fluorescence. First, knowledge of the spore structures important in the staining process could elucidate stains that may be used to detect both total and viable spores. Second, learning the basis for this weak staining might suggest ways to eliminate it. This might be especially helpful in using dyes that may provide information regarding membrane potential. Finally, knowledge of the components giving rise to spore autofluorescence might lead to methods to eliminate this. Consequently, we have undertaken to learn more about spore fluorescence properties, focusing primarily on the large proteinaceous spore coat and primarily using spores of Bacillus subtilis. Two techniques were used in acquiring this information. Fluorescence microscopy was used to detect autofluorescence or staining of dyes bound to B. subtilis spores that lack some (cotE or gerE) or almost all (cotE gerE) coat protein. In addition, flow cytometry was used to detect membrane potential using a membrane potential-sensitive dye, DiOC6(3), and a protonophore, FCCP. This work provided strong evidence that: 1) the autofluorescence of dormant spores is due mainly to the coat; and 2) some fluorescent dyes also bind to the spore coat, although at least two dyes may bind primarily to the cortex. We have further demonstrated that dormant spores of B. subtilis and B. megaterium appear to have no detectable membrane potential, in contrast to in germinating and outgrowing spores. This observation may allow testing of spore viability by assessing membrane potential in germinating spores.

Pulmonary anthrax results in mortality within a few days of exposure even when taking aggressive antimicrobial therapy. Bacillus anthracis, the causative agent of anthrax, is theorized to disseminate away from the lung to initiate the infection in the host. To date this dissemination process remains unclear. In this study we focus on one potential route - the dissemination of B. anthracis via alveoli/airway epithelial cells. Previously, we confirmed that B. anthracis could translocate across a barrier of A549 cells (human lung epithelial cell line) in the absence of professional phagocytes. The translocation did not cause any apparent disruption of the barrier integrity, suggesting a transcellular migration route (Russell et al., Cellular Microbiology, 2008). Additionally, we have shown that members of the Src family protein tyrosine kinases (SFK) are required for the internalization of B. anthracis spores by epithelial cells. Here, we demonstrate that SFK inhibitors PP2 and SU6656 can significantly inhibit spore [B. anthracis Sterne Strain (PXO1+ PXO2-)] translocation across an A549 cell barrier. In contrast, PP3, a negative control compound of PP2, did not have any effect on translocation. Neither inhibitor altered the growth of B. anthracis in the tissue culture media compared to the no inhibitor control. Treatment of cells with PP2, SU6656 or PP3 did not cause any significant change in the barrier integrity as assessed by FITC-dextran migration. Finally, the inhibitory effect of PP2 and SU6656 requires an intact A549 barrier. Taken together, these results demonstrate conclusively that B. anthracis translocates across a lung epithelial barrier via a transcellular route involving activities of SFK.
Leishmania braziliensis can cause cutaneous leishmaniasis (CL) and mucosal leishmaniasis (ML) in humans, and the latter is characterized by excessive T- and B-cell responses. We hypothesized that conversion from CL to ML is partially due to an imbalanced production of proinflammatory and regulatory cytokines, leading to exacerbated host responses to the parasite. To test this hypothesis, we first examined the -2518 single nucleotide polymorphism (SNP) of the MCP-1 promoter because its G/G genotype is known to be associated with autoimmune disorders and infectious diseases. We genotyped 142 Peruvian subjects (18 controls, 65 CL and 59 ML patients) using PCR-RFLP on genomic DNA. Our pilot studies suggested that the MCP-1 G/G genotype appears more commonly in ML patients (28/62, 45%) than either the A/A (9/22, 41%) or A/G genotypes (22/58, 38%) in the same population. These studies also suggest a trend that the G/G phenotype is more commonly observed in CL and ML patients than in healthy controls. Using dot blot analysis, we detected higher levels of MCP-1, IFN-gamma, IL-8, IP-10, MIP-1beta, MIP-1delta, and soluble TNF receptors in the sera of CL and ML patients when compared to healthy controls. Additional quantitative studies confirmed that sera of ML patients contained significantly higher levels of IP-10, MIP-1beta and sTNFRII when compared to CL and healthy controls. This study suggests that the over-production of inflammatory cytokines is a contributing factor to the pathogenesis of mucosal lesions. Studies are ongoing to define the cellular sources of these and other inflammatory mediators and to test whether additional genotypes are also associated with specific clinical manifestations and/or disease prognosis in leishmanial infection in Peru.

Poster 81
URINARY NEUTROPHIL GELATINASE ASSOCIATED LIPOCALIN IDENTIFIES TUBULAR DISEASE IN HIVAN
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BACKGROUND: HIV-associated nephropathy (HIVAN), seen in advanced HIV, is characterized by nephrotic syndrome and rapid progression to end-stage renal disease (ESRD). Clinical diagnosis of HIVAN can be difficult, so kidney biopsy remains the gold standard for diagnosis as serum creatinine typically rises late in the disease course. Biomarkers that could obviate the need for bx and allow for early diagnosis are desperately needed. Neutrophil Gelatinase associated Lipocalin (NGAL) is a protein produced by kidney tubules in response to damage. The characteristics of NGAL are not known in either HIV or HIVAN. OBJECTIVE: We sought to determine whether NGAL was expressed in humans with HIVAN, as well as gene expression and site of NGAL production in a mouse model of HIVAN. METHODS: HIVAN patients were identified from a database of patients with biopsied HIVAN. 13 patients with HIVAN were race-matched to 24 HIV+ control patients without HIVAN with normal kidney function (GFR>60 mL/min and no proteinuria.) uNGAL was measured by immunoblot and standardized by urine creatinine. PCR and in-situ hybridization were used to quantify and localize NGAL gene expression in the Tg26 HIV-transgenic mouse model of HIVAN (HIV-tg). RESULTS: uNGAL levels were significantly elevated in HIVAN patients compared to controls (748 (1160) vs 68(98), p<0.001). Serum creatinine was also elevated in the HIVAN group (5.3(6.1) vs 0.8(0.2), p<0.001). 2 patients with HIVAN had dramatically elevated uNGAL (1286, 420) despite normal serum creatinine (0.9 and 1.2 mg/dL respectively). NGAL gene expression in kidneys of HIV-tg and wild-type (wt) littermates show 62- and 109-fold increases at 6 and 8 weeks. After GC-RMA normalization of gene arrays from both HIV-tg and wt mice, NGAL was significantly upregulated (HIV-tg vs wt, p=1.4X10^-70). In situ hybridization shows NGAL RNA expression in aquaporin 2+ collecting ducts of HIV-tg mice, and prominent NGAL expression in dilated microcystic tubules. CONCLUSIONS: uNGAL is significantly elevated in HIVAN patients compared to HIV+ controls and may identify HIVAN in patients with normal serum creatinine. In a mouse model, we discovered massive gene upregulation and localized the site of NGAL production to the collecting duct microcysts. Measurement of uNGAL may provide rationale for biopsy and aggressive anti-retroviral therapy to prevent progression to ESRD.
MINIMAL LOSS OF AUDITORY AND VESTIBULAR FUNCTION IN COCH KNOCK-OUT MICE

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One of the most prevalent proteins of the inner ear is cochlin, which is encoded by the coagulation factor C homolog (COCH) gene. Mutations of COCH produce a nonsyndromic, progressive, sensorineural hearing loss with vestibular pathology, called DFNA9. It is hypothesized that COCH mutations affect cochlin protein interactions within the extracellular matrix. Previous studies with a knock-in mouse strain has shown progressive loss of inner ear function at 11 months of age. Using a Coch knock-out mouse model (+/+, +/-, and -/- genotypes), auditory and vestibular functions were examined at 13 to 14 months of age to determine gene function in the inner ear. Auditory function was tested with distortion product otoacoustic emissions (DPOAE) and auditory brainstem response (ABR). Vestibular function was evaluated with vestibular evoked potentials (VsEP). DPOAEs were robust and present at all frequencies. ABRs revealed thresholds averaging near 50 dBpeSPL at most frequencies for all genotypes. VsEP thresholds averaged -7.5 dBre:1g/ms for +/- and +/- and were -8.25 dB for homozygous knock-out mice (-/-). Overall, results were not significantly different between the three genotypes of the knock-out mice strain which suggests that knock-out mice do not have significant auditory or vestibular loss at this age. Further testing may be warranted at advanced ages to assess if any progressive loss occurs as it does in the knock-in strain.

MOLECULAR MECHANISMS UNDERLYING EARLY COCAINE MEMORIES

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Early learning events in the progression of cocaine use to dependence can be modeled using the single-trial conditioned place preference (CPP) paradigm. Identifying the molecular neuroadaptations that underlie this persistent memory is critical to understanding the ability of cocaine-associated environments to stimulate craving and relapse in humans. Altered phosphorylation and expression of p42/44 MAP kinase (ERK) and the AMPA glutamate receptor subunit 1 (GluR1) in several brain areas has been suggested as critical to memory development and expression. To test the hypothesis that these neuroadaptations are critical early cocaine learning events, we investigated the expression and phosphorylation of ERK and GluR1 in total homogenate and synaptosome-enriched fractions of brain tissue isolated from rats behaviorally described to express a single-trial cocaine CPP. Male rats were conditioned with a single pairing of cocaine (20 mg/kg) or saline (1 ml/kg) in an unbiased CPP apparatus and sacrificed immediately following a 15 min test session. Western blots were used to detect the expression level of total and phosphorylated (activated) GluR1 and ERK in each fraction. Animals conditioned with cocaine that met a statistically verified CPP criterion spent significantly more time in the cocaine-paired chamber (448 ± 35 sec, mean ±SEM) upon test than did control animals (249 ± 30 sec, p<0.01) or animals treated with cocaine that did not meet criterion (293 ± 15 sec, p<0.01). In total homogenate and synaptosome-enriched fractions isolated from the PFC, we observed no changes in the activation or expression of ERK but decreased expression of GluR1 protein in all rats conditioned with cocaine, regardless of CPP expression (p<0.05 vs. control). In the synaptosome-enriched fraction isolated from the hippocampus, a trend (p=0.07) towards decreased ERK phosphorylation was seen in rats that expressed a cocaine CPP; no other changes were observed. No differences were observed in the fractions isolated from the amygdala. These data suggest that the molecular neuroadaptations that occur in this model of early cocaine associated memory are subtle. Identifying these neuroadaptations involved in early learning is critical to developing new medications to support abstinence from cocaine taking in the face of environmental triggers.
Poster 84
NEUROPROTECTIVE EFFECT OF PEROXIREDOXIN 6 AGAINST HYPOXIA-INDUCED RETINAL GANGLION CELL DAMAGE
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Background: Hypoxia-induced physiological and pathological insult to neuronal cells is implicated in the etiology and progression of various neurodegenerative disorders. Retinal ganglion cell (RGC) death associated with changes in optic nerve head has been implicated in glaucomatous optic neuropathy and hypoxia induced activation of NF-kB is defined as one of the causes for RGC death. Peroxiredoxin 6 (PRDX6), a moonlight protein, protects cells from membrane, DNA and protein damage, and is highly expressed in RGCs protecting the cells from various stressors. We hypothesized that reduced expression of PRDX6 during hypoxia is a causal for RGCs death. Objective: The aim of this study is to investigate the protective role of PRDX6 against hypoxia-induced cell death and its correlation with NF-kB activation by using RGC-5 cell line derived from rat retina. Methods: A construct containing a green fluorescent protein (GFP) linked to Prdx6 cDNA or its mutant at Cysteine(C) 47, redox-active site, was engineered, and was used to generate RGC-5 cells overexpressing PRDX6. These cells were cultured in DMEM with or without serum supplement and kept in a closed hypoxic chamber (1% oxygen) for 24 and 48 hrs. The cells kept under normoxic condition were served as control. Cell viability was determined by MTS assay and apoptosis by TUNEL assay. Intracellular redox levels were measured with fluorescent dye, H2-DCFH-DA dye. Expression of PRDX6, NF-kB and ß-actin was monitored by Western analysis and RT-PCR. Results: RGC-5 cells cultured in a closed hypoxic chamber (1% oxygen) showed 50-60% cell death after 48 hrs of exposure. In contrast, cell death was significantly reduced to 26-32% when cells were over-expressed with PRDX6. This observed cell death was apoptotic cell death, as determined by Tunnel assay and these cells harbor higher levels of reactive oxygen species (ROS) and lower levels of PRDX6. Western analysis revealed the activation of NF-kB in these cells and that was reduced by overexpression of PRDX6. Conclusion: Findings reveal that PRDX6 has neuroprotective effects against hypoxia-induced retinal cell damage, and that this effect may be related to deactivation of NF-kB pathway by PRDX6. PRDX6 may lead to a novel therapeutic strategy to reduce hypoxia-induced retinal ganglion cell death. In future, we will unveil the underlying mechanism of PRDX6 regulation in neuronal cells that may, in turn, lead to develop inductive therapy to activate Prdx6 gene.

Poster 85
EFFECTS OF LONG-TERM SENSITIZATION ON BITING BEHAVIOR IN APLYSIA CALIFORNICA
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Learning and memory modulate the ways an organism expresses its behaviors. The marine mollusk Aplysia californica is an excellent model system for studying learning-induced behavioral modifications and their underlying cellular mechanisms. A well-examined form of learning is sensitization, by which an animal learns and remembers the properties of a noxious stimulus. Although it is well known that sensitization potentiates Aplysia defensive reflexes, its effects on other behaviors, such as biting behavior, have not been determined. Aplysia biting behavior is critical for the animal's survival and relies on a well-characterized neural circuit, which is suitable for cellular analysis. The goal of this project was to explore the effects of a long-term form of sensitization (LTS) on biting behavior. My hypothesis was that LTS would cause a suppression of biting behavior for at least 24h. Two groups were used: an experimental group, which was trained by receiving repeated noxious stimuli (electrical shocks) and an untrained control group. The effects of LTS on biting behavior were analyzed using a seaweed extract (SWE) to measure latency to bite and number of bites. For all animals, SWE was used to provide a constant food stimulus to elicit bites. Duration of the tail-siphon withdrawal reflex (TSWR) served as an index to assess the occurrence of LTS. The duration of the TSWR and the expression of biting behavior were measured before and 24h after training. Trained animals showed a significant increase in the duration of the TSWR 24h after training compared to untrained animals, which indicates that memory for sensitization was formed in the experimental group. In addition, the LTS-trained group showed a significant decrease in the number of bites compared to controls after 24h. These results indicate that LTS suppressed biting behavior 24h after training. This experiment addresses how learning alters the animal's behavioral repertoire by examining the effects of a simple form of learning (sensitization) on the expression of two different behaviors both essential for the animal's survival (biting and defensive withdrawal). Importantly, these findings lay the foundation for the analysis of the cellular mechanisms underlying the LTS-induced suppression of biting behavior in Aplysia. In the future, I intend to explore the effects of LTS training on the activity of neuron B51, which is a key element in the neural circuit controlling biting behavior.
Poster 86

AN EVALUATION OF THE EFFECT OF AGE ON HUMAN MOTOR CORTICAL ELECTROPHYSIOLOGY
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Background: Electrophysiology studies have contributed significant insights to our understanding of the central nervous system. Electroencephalography (EEG) is a common non-invasive way to study the human cerebral cortex but has limited spatial and spectral resolution. Electrocorticography (ECoG) largely avoids these limitations by placing electrodes directly on the surface of the brain. As ECoG studies are currently applied for clinical and research applications in adult and pediatric patient populations, it is necessary to understand how the cortical electrophysiology differs with age among patients. Objective: To investigate the differences in cortical electrophysiology associated with age through analysis of power spectral density changes as measured by ECoG.

Methods: Patients implanted with ECoG electrodes for neurosurgical evaluation of partial epilepsy were asked to perform a repetitive hand motor task consisting of alternating rest and activity trials. Signals from electrodes placed over sensorimotor cortex and neighboring areas were recorded and associated in time with the task state. Changes in the signals’ power spectral density associated with activity trials were used to identify areas of cortex being activated with the motor task. These areas of activation were then compared across patients and correlated to patient age. Results: A larger area of cortex showing low-frequency power decreases was observed with increasing patient age. In contrast, the area of cortex showing high-frequency power increases did not significantly differ with age. Conclusions: Event related low-frequency power decreases and high-frequency power increases are believed to be caused by different underlying physiologic processes. Low-frequency changes are thought to represent thalamocortical projections and synaptic potentials, while high-frequency changes are thought to represent small cortical neuronal populations and action potential firing rates. The unchanging nature of high-frequency activations likely indicates that the cortical neuronal population utilized for a task does not change with age. The enlarging cortical representation of low-frequency changes, however, could represent enhanced thalamic projections and broader synaptic networking with the task as the brain ages. Therefore, in a clinical or research application that intends to make use of these features, high-frequency activations measured by ECoG may be a more reliable measure across age ranges.

Poster 87

CEREBRAL FUNCTIONING IN CHILDREN WITH ADHD UNDER ATOMOXETINE TREATMENT
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Background: Attention-deficit hyperactivity disorder (ADHD) is described as a very common condition among school-aged children (7%). The main etiologic hypothesis of ADHD is a dopaminergic malfunctioning. Many neuroimaging studies, mainly those using H-Magnetic Resonance Spectroscopy (MRS), show a difference in the concentrations of metabolites in children with ADHD in the cortical-striatal-cerebellum pathway. However, results tend to differ from one study to another. These contradictions may be caused by the different medications used for ADHD treatments in the different studied population. The effects of medication, mostly those of atomoxetine (Straterra), on neurometabolite concentrations are poorly documented. Objective: The goal of this study is to examine the influence of atomoxetine on the cerebral functions of children suffering from ADHD. Methods: Participants: Three groups of children aged between 5-12 years old participated in the project: (1) children with ADHD (DSM-IV criteria) who have never been on any pharmacological treatment for ADHD (n=13), (2) children with ADHD who were under atomoxetine treatment (n=11) and (3) a control group with children without ADHD diagnosis. Imaging: The H-MRS study was realized on 5 cerebral regions: bilateral prefrontal cortex, bilateral striatum and left cerebellum. The biochemical markers, used under their absolute form, were: N-Acetyl-aspartate (NAA), glutamate-glutamine (Glx), choline (Cho) and creatine. Statistical analysis: Covariance analysis and post-hoc tests (LSD) were used. Results: Significant differences between groups in choline concentrations were found in the left prefrontal cortex [F(2,24)=3.993, p=.032)], the right prefrontal cortex [F(2,24)=5.971, p=.008)] and the right striatum [F(2,24)=3.382, p=.051]). In these three areas, choline concentrations were higher in children with ADHD under atomoxetine treatment than in children with ADHD without medication. Choline concentrations were also higher in ADHD with medication than in controls in the prefrontal cortex. Glx concentrations in the left striatum tend to be lower in the two groups of patients (with and without atomoxetine treatment) than in the control group. Discussion and conclusion: Atomoxetine seems to influence choline concentrations in the fronto-striatal pathway in children with ADHD, which can be linked to the amelioration of their cognitive abilities.
Poster 88

DISSECTING FEEDING REGULATING CENTRAL CIRCUITS OF HYPOTHALAMIC MCH NEURONS
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Chemosensory signals have been shown to robustly regulate a variety of physical activities. Recent studies have revealed an important role of a neuropeptide called melanin-concentrating hormone (MCH) expressed by a unique group of lateral hypothalamic neurons in regulating feeding. To dissect and characterize the structure of the neural circuits underlying the effects of MCH neurons in regulating feeding, we made recombinant adeno-associated virus (rAAV) to selectively express a retrograde transsynaptic tracer, GFP-TTC (tetanus toxin fragment C), in MCH neurons. The results show that MCH neurons are regulated by two types of neural inputs: cortical as well as hormonal signals. Sensory as well as frontal and parietal cortices send massive inputs to the MCH neurons, whereas hormonal signals reach MCH neurons indirectly via a relay through hypothalamic arcuate neurons. Surprisingly, the olfactory and gustatory inputs originate only from deep layers of the anterior olfactory nucleus, the piriform cortex and gustatory cortex, suggesting MCH neurons receive highly processed chemosensory inputs. As MCH can potently regulate appetite and brain reward pathways, these studies reveal that the lateral hypothalamic MCH neurons integrate both direct sensory and highly processed cognitive neural inputs as well as internal homeostatic signals to regulate stereotyped behavioral responses.

Poster 89

EVIDENCE OF ALTERED PSYCHOSOCIAL BEHAVIOR AND COMPROMISED STRESS RESPONSE FOLLOWING ‘MINOR’ STROKE IN THE RAT
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Despite vast heterogeneity in size and region of infarction, a stroke is considered ‘major’ if it results in lasting motor impairments or aphasia. In contrast, patients that regain a near-normal ability to walk and speak are designated as having a ‘minor’ stroke and discharged without continuing care, despite enduring mental fatigue, emotional lability, anxiety, or compromised capacity to cope with stress- all of which impinge on quality of life. Importantly, for strokes that spare motor regions, emotional and cognitive impairments may be the forefront of concern. In the present study we examine the ability of rodents to cope with psychosocial stressors following non-motor (‘minor’) stroke. Groups of male Sprague-Dawley rats were handled daily for one week prior to sham surgery or focal ischemia of the left cingulate cortex. After recovery subjects were randomized to control handling or CMS for 3 weeks. Social observation was used to determine dominance. Behavior testing followed intermittently for five months. In a subset of animals cingulate cortex lesions did not cause fine or gross motor deficits. Hyperarousal and habituation-behaviors sensitive to psychosocial stressors- were tested using an open field for ten-minute trials 1 month post-stroke with repeated exposure 1, 2, 4 and 8 weeks later. Subordinate animals were hyperactive compared to dominant cage mates, but minor stroke induced hyperarousal irrespective of dominance. Minor stroke, but not CMS, significantly attenuated habituation over repeated trials. Defecation rates- an index of hypersensitivity to stress-revealed that the combination of minor stroke with CMS treatment caused higher defecation frequency in subordinate rats. Additionally, cingulate cortex lesions slowed strategy acquisition in the Morris water maze (a stressful learning task), caused emission of more distress vocalizations, and porphyrin hypersecretion. Interestingly there were no differences in long-term memory. These observations are consistent with panic-like behaviors suggesting stress hormones may also be affected. Assays of hypothalamic-pituitary-adrenal axis function indicated impaired corticosterone signaling. Collectively these findings suggest that ‘minor’ stroke can result in biological vulnerability to stress. Given an established model and sensitive outcome measures, research can begin to probe neural mechanisms and optimal treatments for sustained biopsychosocial disturbance following non-motor stroke.
Oxidative stress (OS), which affects all body tissues, can cause cellular damage and ultimately apoptosis. The eye is exposed to a high oxygen tension and bright light, both of which can cause OS on the retina. The mechanisms of OS are of particular interest in the codependent relationship between the retinal pigmented epithelium (RPE) and the photoreceptors due to their implication with pathologies such as retinitis pigmentosa. It has been established that OS initiated by TNF-α and H2O2 induces changes in pro and anti-inflammatory protein expression in RPE cells. Docosahexaenoic acid, which is a lipid located in the cell membranes of RPE cells, is induced by neurotrophins to produce Neuroprotectin D1 (NPD1). These neurotrophins play an important role in modifying the expression of pro-inflammatory genes in OS environments through the induction of the endogenous NPD1 pathway. This project will test the amount that certain neurotrophins downregulate the expression of pro-inflammatory proteins and promote cell survival and homeostasis. The neurotrophins persephin, BDNF, LIF, FGF-B, and PEDF will be added to a cell culture of human RPE cells prior to the induction of OS followed later by Western blot analysis to follow relative changes in the abundance of the pro-inflammatory proteins. Upon introduction of BDNF the amount of the pro-inflammatory gene CEX-1 was reduced by 55% while the pro-inflammatory protein IL-1ß was reduced by 65%. Similar results were found when introducing the neurotrophin PEDF; CEX-1 was reduced by 93% and IL-1ß was reduced by 51%. These results demonstrate that neurotrophins are key agonist in the synthesis of NPD1, a mediator that in turn, promotes homeostatic survival in human RPE cells. Further progression of the project will include the introduction of other neurotrophins and the analysis of their effects on the expression of other pro-inflammatory proteins.

This research study focused on the action of systemically injected NPD1, a neuroprotective derivative of docosahexaenoic acid, on choroidal endothelial cell ramification in laser-induced CNV. CNV was achieved using an ophthalmic laser attached to a slit lamp. Three 50 micron diameter lesions were made on each fundus of anesthetized mice. NPD1-treated mice were injected intraperitoneally with 2.85 µL/25 g body weight of NPD1 in saline one hour prior to laser exposure and then returned to their cages following laser damage. Controls received only saline. All mice were again injected on four subsequent days: one, three, five, and seven days after laser damage. After 7 or 14 days the mice were sacrificed, their eyes collected, and the retina was removed to produce an eyecup. Immunohistochemistry was performed to selectively label actin, microglia, nuclei, and endothelial cells. Eyecups were then flatmounted onto glass slides and confocal microscopy performed. Images were analyzed (ImageJ software) to obtain pixel counts of the labeled endothelial cells. In 7 day control mice (n=7), the area of endothelial cell growth had an average pixel count of 261,181 pixels, while 7 day NPD1-treated mice (n=7) had an average pixel count of 138,429 pixels (53% decrease). Control mice had an average pixel count of 205,897 pixels at 14 days, while 14 day NPD1-treated mice had an average pixel count of 69,463 pixels (66% decrease). These results indicate that there is decreased angiogenesis after laser-induced CNV in NPD1-treated mice.
Poster 92
Analysis of Tobacco Mosaic Virus(TMV) on Primary and Metastatic Human Colon Cancer Cells treated with α-Lactalbumin or Sulindac
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Background: Colon cancer is the second most frequent reason in the cancer-related deaths in the world. It is reported that colon cancer is the 3rd most frequent cancer in males and the 4th most frequent cancer in female. During cancer therapy, the correct time and correct medicine is crucial for different patients. In addition, the primary and metastatic colon cancer therapy may also be different because of cancer cell behavior. We have investigated the TMV has efficiency on the medicine during treatment of cancer cells. Methods: Colo-320 and Colo-741 lines were used in this study. The cells were cultured in RPMI-1640 media including %10 FCS, %1 L-glutamine and %1 penicillin-streptomycine. After 24 hours of culture, the cells were treated with either α-lactalbumin or sulindac or α-lactalbumin+TMV or sulindac +TMV. Also the cells were cultured with TMV only. After 24 hours of treatment, culture mediums from all groups were collected for cytotoxicity analysis, the cells from all groups were fixed in %4 paraformaldehyde for 30 minutes for histochemical analysis. Cell cytotoxicity were evaluated with ELISA. Cell death was investigated using TUNNEL assay. Results: The Colo-320 cells were semi-adhesive cells; the Colo-741 cells were attachment cells. After treatment with sulindac of Colo-320 cells, the number of alive cells was less when compared with other groups. In addition, α-lactalbumin+TMV treated Colo-320 cells were also less than both only α-lactalbumin and only TMV applied groups. It was also observed that the number cells in Colo-741 cells which were treated with only α-lactalbumin or only sulindac groups had less cell amount than the other groups. The TUNEL positive cells were detected in all groups. However, there were more apoptotic cells in Colo-320 treated with both α-lactalbumin and α-lactalbumin+TMV applied groups. The higher number of apoptotic cells were detected in Colo-741 cells which were treated with α-lactalbumin+TMV.

Conclusion: Our result suggests that both primary and metastatic cells were much more affected when TMV during treatment. However, the addition of TMV during treatment protocols may cause differences in drug interactions with cells. In farther researchs, TMV can be used to recombine according to suitable receptor in cancer cells by gene therapy researchs. Simultaneously, TMV might be used to treat with different medicines of other cancer types. Researchs are still going on about this issue in our faculty.

Poster 93
MECHANISMS FOR THE DOWN-REGULATION OF MICRORNA-137 IN MELANOMA
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BACKGROUND: microRNAs (miRNAs) are a class of non-coding RNA that negatively regulate gene expression by binding to messenger RNA. miRNA-137 has been shown to be down-regulated in cancer but the mechanism for its down-regulation is not completely understood. We recently showed that miRNA-137 might function as a tumor suppressor by inhibiting the expression of the melanoma oncogene microphthalmia-associated transcription factor (MITF). We also identified a variable number tandem repeat (VNTR) within the transcription start site of miRNA-137 and found that a melanoma cell line with twelve repeats has increased MITF protein expression as compared to a cell line with three repeats. OBJECTIVE: The purpose of this study was to determine the mechanism of down-regulation for miRNA-137. We propose that an expansion of the VNTR may cause down-regulation of miRNA-137 by two different mechanisms. First, we hypothesize an expansion of the VNTR may alter the splicing of the primary miRNA-137 transcript by the endonuclease Drosha. Second, we hypothesize that an expansion of the VNTR, which is rich in CpG dinucleotides, may become hypermethylated in cancer cells resulting in suppression of miRNA-137 transcription. METHODS: To test our first hypothesis, we preformed an in vitro miRNA processing reaction using purified Drosha and primary miRNA-137 transcripts with three or twelve repeats. We compared the processed transcripts by bioanalyzer and sequencing analysis. To test our second hypothesis, we demethylated melanoma cells lines with 5-aza-2'-deoxycytidine and measured the miRNA-137 expression by qRT-PCR. Finally, we performed a bisulfite genomic sequencing analysis on melanoma tissue samples and adjacent normal skin to determine the methylation status of the miRNA-137 gene. RESULTS: Our preliminary data suggests that while Drosha successfully processes both the three and twelve VNTR transcripts, the twelve VNTR transcript is processed with less efficiency. We also show that the miRNA-137 expression is upregulated following demethylation in some cell lines and that miRNA-137 expression is reduced in melanoma tumors when the gene is hypermethylated. CONCLUSION: Expansion of a VNTR upstream of the tumor suppressor miRNA-137 may contribute to its down-regulation in melanoma.
OVEREXPRESSION OF EYES ABSENT HOMOLOGY 4 (EYA 4) IN MALIGNANT PERIPHERAL NERVE SHEATH TUMOR CELLS ALTERS THE RETINAL DETERMINATION TRANSCRIPTION COMPLEX AND PROMOTES TUMORIGENESIS
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Background: NF1 is an autosomal dominant disorder affecting approximately 1 in 3500 individuals worldwide. NF1 patients are at risk for malignant peripheral nerve sheath tumor (MPNST), a life threatening sarcoma. The NF1 gene product, neurofibromin, is one of a family of GTPase activating proteins (GAPs) that accelerates the hydrolysis of active Ras-GTP to inactive Ras-GDP. MPNST cells have high Ras-GTP and elevated EGFR. EGFR and HRas inhibitors slow growth of MPNST cell lines, supporting the idea that dysregulation of these signaling pathways may contribute to tumorigenesis. Objective: dissect the mechanism of transformation, test the hypothesis that overexpression of EYA4, a transcription factor, contributes to tumorigenesis. Methods: microarray analysis was carried out between MPNST vs. normal human Schwann cells. shRNA is used to knockdown the target gene expression and Xenograft is used to verify the knockdown effect on tumorigenesis. Results and Conclusion: EYA4, a transcription factor with phosphatase activity, was upregulated 37 fold in MPNST. To test the hypothesis that EYA4 overexpression is related to tumorigenesis via Ras or EGFR signaling, we knocked down EYA4 in MPNST cells using shRNA and studied expression of EYA4 and its binding partners DACH and SIX1 upon Ras and EGFR activation or suppression. EYA4 knockdown slowed cell growth, reduced cell proliferation and caused cell death. Cell migration was reduced and tumorigenesis profoundly reduced when EYA4 knockdown stable cells were injected into athymic nude mice. An EGFR selective inhibitor and dominant negative HRas reduced EYA4 and SIX1 expression and induced DACH expression, implicating the EYA4-DACH-SIX1 complex in NF1 tumorigenesis.

LOW-FAT DIET REDUCES THE PROGRESSION OF PREVIOUSLY ESTABLISHED BONE METASTASES IN MICE
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Introduction: With an incidence of ~220,000/year and a lifetime risk of ~20%, Adenocarcinoma of the Prostate (CaP) is the #1 noncutaneous malignancy and the #2 cause of cancer-related death in American men. Almost one-third of CaP patients develop metastases (mets), most commonly to bone, which doubles both the risk of overall fractures and the cost of treatment. Currently, median survival with bone mets is 21-33 months. Compelling clinical data from recent cohort studies suggest that low-fat diet may reduce mortality in metastatic adenocarcinoma of the breast and colon, but no such data exist for CaP bone mets. Methods: Based on previous protocols for establishing bone mets, we injected 60 athymic NCr-nu/nu male mice with 0.5-2 x 10^6 ARCaPE cells intratibially. Mice were randomized to receive either a low-fat (LF: 10% fat) or Western diet (WD: 40% fat). Mice were fed a modified paired feeding protocol, and weights and caloric intake were measured biweekly to ensure equal caloric intake across all groups. Thirty mice (15 from each group) were sacrificed after 12 weeks, to determine actual tumor size at the same time point. Remaining mice were sacrificed once their tumors reached 1100 mm^3. Results: LF and HF mice consumed an equal number of calories throughout the experiment and consequently maintained statistically identical body weights. 12 weeks after tumor injection, bone mets in LF mice were 33% smaller than in WD mice (p=0.06). Additionally, LF mice on average had a 20% longer survival than WD mice (p=0.06). Conclusions: These data suggest that low-fat diet may reduce the progression of established bone mets, a novel finding which may provide hope and opportunity to patients afflicted with bone mets. Further studies to increase our sample size, as well as histomorphometry and immunohistochemical investigations into the molecular mechanisms behind the interactions between dietary fat and CaP bone mets are also underway and will be completed well before the NSRF.
Predicting Recurrence After Radical Prostatectomy: Does Age Matter (And When)?
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Background and Objective: Preoperative PSA level, Gleason score, and tumor stage have all been shown to influence risk of recurrence after radical prostatectomy. Increasing age has been associated with more indolent behavior in some cancers. This study evaluates the effects of age at surgery on recurrence-free survival in prostate cancer patients at a single institution stratified by established preoperative risk factors. Methods: Using our institution's urologic oncology database, a retrospective analysis of 3,736 men treated with open or robotic-assisted laparoscopic radical prostatectomy for prostate cancer from 1988 to 2008 was conducted. Patients were divided into two groups by age at the time of surgery, and recurrence-free survival rates were analyzed using Kaplan-Meier survival curves. The subgroups were stratified by preoperative PSA level, biopsy Gleason score, and clinical stage; multivariate analyses with cox proportional hazards models were used to further identify independent predictors of recurrence. Recurrence was defined as a single PSA level of 0.2 ng/ml or greater at least 28 days after surgery. Results: 1,984 patients were divided into groups 1 (n=1,325 age 40-64) and 2 (n=659 age =65). Five-year recurrence-free survival rates were 80.6%(CI: 78.0-82.9%) and 75.6%(CI: 71.5-79.1%) for groups 1 and 2, respectively. In the univariate model, advanced age was significantly associated with an increased overall risk of recurrence (HR 1.30, p=0.012). However, in multivariate analyses accounting for PSA, Gleason score, and clinical stage, age was not shown to be an independent predictor of recurrence (HR 1.04, p=0.76). In a subset of patients with low-grade cancer (Gleason score 2-6), advanced age was associated in a univariate analysis with an even greater relative risk of recurrence (HR 1.47, p=0.032). However, this was not significant in the multivariate model (HR 1.27, p=0.21). Conclusions: Older patients who undergo radical prostatectomy for prostate cancer appear to have an increased risk of recurrence, which is most notable in patients with low-grade disease. However, age is not an independent predictor of recurrence when accounting for PSA, grade, and stage.

Poster 97
PI-103 AND RAPAMYCIN SYNERGISM ABROGATE RESISTANCE TO mTOR INHIBITION IN PRE-B ALL
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mTOR integrates multiple signaling cascades to act as a critical mediator of lymphocyte survival and proliferation. The mTOR inhibitor (MTI) rapamycin (rap) suppresses proliferation and induces apoptosis of pre-B ALL in vitro and in human ALL xenografts, although lymphoid growth factors such as IL7 can overcome these effects. We hypothesized that PI3K inhibition would potentiate the action of MTI by blocking growth factor signals upstream of mTOR. PI-103 is a dual MTI and class I PI3KI. In contrast to rap, which selectively inhibits mTOR Complex (TORC) 1, PI-103 inhibits both TORC1 and TORC2. To evaluate the targeted inhibition of PI3K, TORC1 and TORC2 with combinations of PI-103 and rapamycin in pre-B ALL. Murine and human pre-B ALL cell lines were treated with combinations of PI-103, rap, and IL7. Growth inhibition and cell death were assessed via MTT proliferation assays and Annexin V flow cytometry, respectively. Post-translational modifications of downstream targets of mTOR such as S6, AKT, and 4E-BP1 were assessed by immunoblotting. PI-103 alone decreased cell proliferation and increased cell death in a dose-dependent manner, with IC50 values of 250 nM and 100 nM for human and murine pre-B ALL cell lines, respectively. Combinations of PI-103 and rap demonstrated synergistic inhibition at IC50 dosing on both human and mouse ALL lines. Additionally, co-treatment with 1 uM PI-103 and 10 ng/ml rap fully inhibited cell proliferation, compared to 40% inhibition with rap alone. This same combination resulted in 50% cell death, versus 15% with rap alone. While IL7 fully reversed rap-mediated inhibition, the addition of 1 uM PI-103 effectively blocked this IL7-mediated reversal. PI-103 + rap also decreased phosphorylation of S6, AKT, and 4E-BP1 more than that achieved with either agent alone. IL7 was able to reverse this effect (increased phosphorylation) when given with rap, but not in the presence of PI-103. Single agent PI-103 and rap both inhibited proliferation and induced cell death in pre-B ALL. However, co-administered PI-103 and rap demonstrated synergistic inhibition and induction of cell death, and also overcame the pro-survival effects of IL7. This suggests the presence of non-overlapping inhibitory effects of these agents on mTOR signaling. Our data support the notion that treatment with combination therapy targeting multiple nodes of the growth factor-PI3K-mTOR pathway could improve efficacy and reduce MTI resistance in pre-B ALL.
CHARACTERIZATION OF SIGNALING PROPERTIES OF THE HCMV-ENCODED G PROTEIN COUPLED RECEPTOR US28 AND ANALYSIS OF CONTRIBUTION TO VIRAL INDUCED ATHEROSCLEROSIS
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The herpesvirus, human cytomegalovirus (HCMV), has been shown to induce vascular smooth muscle migration, and therefore, is a likely contributor to the development of vascular disease. Atherosclerosis involves a sequence of inflammatory events that ultimately result in a narrowing of the walls of arterial vessels by the formation of fibrous plaques. The release of chemoattractant molecules (such as RANTES) by LDL engorged macrophages and the subsequent migration of smooth muscle cells from surrounding areas into the vessel intima is associated with the formation of an advanced atherosclerotic lesion. It has been demonstrated that this process is augmented by infection of surrounding smooth muscle cells with HCMV, and therefore, the expression of viral gene products is implicated in the formation of vascular disease. HCMV encodes a G protein-coupled receptor (GPCR), US28, that demonstrates various modalities of cell signaling, including activation of phospholipase C-ß and release of calcium from intracellular stores. The US28 gene product is the suspected culprit of HCMV-associated atherosclerosis, as US28 activity has been demonstrated to result in arterial smooth muscle cell migration. In this study we have investigated the signaling properties of various US28 mutants in smooth muscle cells infected with HCMV. Interestingly, the N-terminal chemokine binding domain is not required for PLC-ß/ IP3 signaling and agonist has no effect. Conversely, this chemokine binding domain and stimulation with RANTES is required for calcium release from intracellular stores. We have also investigated the effects of US28 on signaling via the endogenous lysophosphatidic acid (LPA) receptor. LPA is a component of oxidized LDL and thus has been demonstrated in growing atherosclerotic plaques. These results have indicated that US28 induces a variety of signaling events in smooth muscle cells; some in response to agonist and some independent of agonist. Moreover, we have demonstrated that US28 can alter signaling via endogenous GPCRs. It remains to be determined how these events contribute to HCMV induced smooth muscle cell migration and subsequent atherosclerosis.

GENETIC REMOVAL OF THE A2B ADENOSINE RECEPTOR FROM ADENOSINE DEAMINASE-DEFICIENT MICE LEADS TO ENHANCED PULMONARY INFLAMMATION AND FIBROSIS
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Adenosine is a signaling nucleoside that is generated in response to cellular injury and orchestrates the balance between tissue protection and the progression to pathological tissue remodeling. Adenosine deaminase (ADA) deficient mice develop progressive airway inflammation and remodeling in association with adenosine elevation, suggesting adenosine can promote features of chronic lung disease. Furthermore, pharmacologic studies demonstrate that A2BR antagonism can attenuate features of chronic lung disease in this model implicating this receptor in the progression of chronic lung disease. The focus of this study was to examine the contribution of A2BR signaling in this model by generating ADA/A2BR double knockout mice. The hypothesis was that genetic removal of the A2BR from ADA-deficient mice would lead to diminished pulmonary inflammation and damage. On the contrary, ADA/A2BR double knockout mice exhibited enhanced pulmonary inflammation and airway destruction. Marked loss of pulmonary barrier function leading to excessive airway neutrophilia was observed and is thought to contribute to the enhanced tissue damage observed. These findings support an important protective role for A2BR signaling during acute stages of lung disease.
Poster 100
VARIATIONS IN PRESENTATION OF CELIAC DISEASE IN ADULTS AND ITS ASSOCIATION WITH OTHER CONDITIONS.
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Background: Celiac disease (CD) is an autoimmune enteropathy triggered by ingestion of gluten in genetically susceptible individuals. It has extremely varied clinical presentations. Though the disease is well described in children, it is often missed in adults by treating physicians due to lack of awareness. Objective: To evaluate the variations in presentation of celiac disease in adults and its association with various conditions. Methods: This retrospective study was conducted by reviewing the file records of the patients admitted during the last 10 years at the Aga Khan University Hospital. Patients diagnosed with celiac disease greater than 15 years of age were included in the study. Diagnosis was established by detecting raised tissue transglutaminase antibodies in serological tests and supportive biopsy findings. Results: A total of 31 patients were included in the study consisting of 61.3% males and 38.7% females ranging from 15 to 51 years of age (mean 27.55 ±9.93). Of the total patients 32% of the patients were found to be underweight (BMI<18.5). Typical presentation with gastrointestinal (GI) symptoms was seen in 71% of the patients, atypical presentation with extra intestinal manifestations in 12.9% and silent presentation with no symptoms was seen in 10.3%. Predominant GI symptoms included diarrhea (in 71% patients), vomiting (in 41.9%), anorexia (in 22.6%) and abdominal pain (in 26%). Predominant extra intestinal manifestations include iron deficiency anemia in 29% of the individuals, vitamin B12 deficiency anemia in 16%, folic acid deficiency anemia in 10%, vitamin D deficiency in 12.9%, osteoporosis and osteomalacia in 3.2% each, renal calculi in 6.4%, arthritis in 3.2%, myopathy in 3.2% and 16% had raised ALT levels. Endoscopies revealed duodenal ulcer in 12.8% patients and gastritis in 35%. Biopsy findings revealed partial villous atrophy in 46.4% of the patients, complete villous atrophy in 35.5%, cryptal hyperplasia in 9.7% and intraepithelial lymphocytosis in 6.5%. H.pylori infection was seen in 48.4% of the patients with CD, irritable bowel syndrome (IBS) in 6.5% and giardiasis in 3.2%. Conclusion: Celiac disease is less common in adults but does exist and may present at any age. It should be looked for in underweight patients and patients with IBS, anemia, vitamin D, B12 and folic acid deficiency, arthritis and other related conditions.

Poster 101
PRE-MICROALBUMINURIA AS A NOVEL CARDIOMETABOLIC RISK CORRELATE
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Background: Microalbuminuria is a marker of endothelial dysfunction and cardiometabolic risk, but it is unknown whether variations in urinary microalbumin excretion within the “normal range” represent differential risks for cardiovascular disease (CVD). Objective: The objective of this study is to test the hypothesis that variations in urinary microalbumin excretion within the “normal range” reflect individual differences in cardiometabolic risk. Methods: The study population comprised age and gender-matched African-American (n=55) and Caucasian (n=46) offspring of type 2 diabetes mellitus parents. We measured microalbumin-creatinine ratios (MCR) and the following CVD risk factors: blood pressure, lipid and lipoprotein profiles, waist circumference, body mass index (BMI), and glucoregulatory parameters. The latter consisted of fasting plasma glucose, insulin, 2-hour OGTT plasma glucose levels, as well as calculated indices of insulin resistance (HOMA-IR), and beta cell function (HOMA-B). We analyzed the relationship between microalbuminuria and the aforementioned cardiometabolic risk factors in our bi-racial cohort. Seven patients with clinically significant MCR (> 30 mg/g) were excluded from the analysis (n=94). Results: There were no significant differences between Caucasians and African-Americans in any of the measured risk factors. The mean MCR was 10.36 mg/g in patients with metabolic syndrome compared to 6.767 mg/g in patients without metabolic syndrome (p<.0008). Regression analysis indicated a clustering of cardiometabolic risk factors among persons with an MCR > 15 mg/g compared to those with MCR < 15 mg/g. Conclusions: Based on our data, an MCR of 15 mg/g or greater may be considered a pre-microalbuminuric state that connotes increased cardiometabolic risk. Pre-microalbuminuria (variations of microalbuminuria in the upper normal range) is a correlate of individual and aggregate cardiometabolic risk factors. Further studies in a larger population would be required to confirm our observations.
DIABETIC GASTROPARESIS – DO DELAYED DIABETICS DIE DIFFERENTIALLY?
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Background: Diabetic gastroparesis (GP) has been associated with high mortality, at risk factors for death are unknown. Objective: Our aim is to identify indicators predisposing this group of patients to death to expedite treatment options. Patients: Over a 10 year period, we evaluated 97 patients (mean age at baseline = 46.2) with diabetic gastroparesis and assessed them for GP symptoms (vomiting (V), nausea (N), early satiety, bloating, abdominal pain, and a total symptom score (TSS) (max score = 4 for each symptom, TSS max score = 20)), quality of life (QOL) based on the investigator-derived independent outcome measure score (IDIOMS) scale, 4 hour gastric emptying time (4hGET), and survival. Within the group there were 31 male, 66 female, 25 African American, and 72 Caucasian participants. During the course of the study, they were treated with diet, medications and in some cases, permanent gastric stimulation systems (permGES). Results: 13 of the 97 patients died (mean age at death = 39.0) (table 1). All 13 had characteristics that separated them from the patients who did not die. Baseline measurements from every patient that died showed significantly (p < 0.05) delayed 4hGET (mean = 46.1±6.65%), impaired QOL (IDIOMS score = 21.1±1.10), and greater vomiting (mean score = 3.67±0.19); however, there was no significant difference in symptoms of N (3.59±0.18) or in TSS (14.41±0.95) (table 2). Furthermore, among the delayed subgroup of patients, there were significant (p < 0.05 by t-tests) baseline differences in three criteria (V, 4hGET, QOL) between those that are deceased and alive (table 2). Surviving patients (mean current age = 49.2 yrs) have survived an average of 43 months since baseline measurements were taken, while the 13 deceased survived an average of 20 months. Conclusions: Subsets of diabetic GP patients presenting with severely delayed gastric emptying, high instances of vomiting, and poor quality of life at baseline appear to be the patients most likely to die. Further efforts may be warranted in the treatment of this subset of patients.

THE ANTIANGIOGENIC EFFECTS OF THE METRONOMIC DOSING OF SWEET LEAF TEA
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Studies from our laboratory have revealed a striking antiangiogenic activity from extracts of Rubus suavissimus (Sweet Leaf Tea; SLT). Other studies suggest that a metronomic dosing schedule (lower dose for an extended period of time) may be a less toxic means of drug delivery than traditional chemotherapeutic schedules. These findings, together with previous work in our lab suggesting potential efficacy with metronomic dosing of Epothilone B led us to consider similar activity with a botanical compound. We hypothesize that SLT will be an effective antiangiogenic agent for human tumors when dosed according to a metronomic schedule. To test our hypothesis, four human cancer samples were assayed in our human tumor angiogenesis model. Minced tissue was embedded in a thrombin-fibrinogen clot using a 96-well plate. Each well was treated with either control media (no SLT), or with extract-containing media at concentrations varying from 1 mg/ml to 0.01 mg/ml for up to 56 day, with thirty wells per treatment. Beginning on day 28, tissue fragments were observed microscopically and evaluated for angiogenic growth. The percentage of wells that initiated an angiogenic response, and the angiogenic index (a semi-quantitative scale of growth, averaged from the 30 wells prepared) was recorded. A dose-dependent inhibition of angiogenesis was observed in 3 of the 4 tumors, but over time no consistent vessel regression with lower doses of SLT (metronomic) was observed. Over time (day 28-56), the change in overall angiogenic index for treatments 0.01, 0.05, 0.1, 0.5 and 1 mg/ml was: +1.6, +1.3, +0.7, -0.02 and -0.09 (Colon Ca LN); -1.7, +0.3, +0.59, +0.05 and +0.2 (Liver Carcinoid); +4.2, +2.8, 0.39 and no growth at 0.5 and 1 mg/ml (Liver Carcinoid); and + 0.25, -0.04, -0.15, -0.10 and -0.14 (Colon Ca) respectively. For each of these values, a “+” indicates angiogenic growth from day 28-56 while “-” indicates regression. Predicated on previous work in our laboratory demonstrating the potential efficacy of metronomic dosing with Epothilone B, these results raise important questions about the nature of metronomic dosing. Future work employing combinatorial therapies will be explored. The toxicity of chemotherapeutic regimens based on maximum tolerable dose principles, combined with recent data refuting the idea of true complete remission induced with standard cancer therapies, leads to the conclusion that other novel avenues of treatment need to be explored.
Background: Strontium (Sr) is an alkaline earth metal with bone seeking properties. Unlike bisphosphonates and PTH, Sr both decreases bone catabolism and promotes bone anabolism. Phase III trials treating osteoporotic patients with Sr demonstrated a 41-49% reduction in vertebral fracture risk and a 16% decrease in non-vertebral fractures. Objective: Utilizing a binge alcohol model that decreases bone mineral density (BMD) and strength in appendicular and axial trabecular bone, we observed the potential of Sr as treatment for alcohol-induced osteoporosis. We hypothesized that Sr, co-administered with binge alcohol simulation in rats, would decrease alcohol-induced bone damage. Methods: Thirty-two male rats were randomly assigned to 4 treatment groups: saline i.p., 3 days/week; binge alcohol, 3g/kg i.p., 3 days/week; SrCl, .25g/kg/day consumed via drinking water; alcohol plus Sr. Alcohol was administered via single daily i.p. injection of 20% ethanol/saline at a dose of 3g/kg to achieve a peak blood alcohol content (BAC) of 300mg/dL. After 4 weeks of treatment whole blood, tibia, femur, and L4 and L5 vertebrae were collected and analyzed for BMD by quantitative computerized tomography, compressive strength-to-failure using an Instron machine, and bone anabolism via enzyme-linked immunosorbent assay (ELISA). Results: In femoral trabecular and femoral neck cortical bone, binge alcohol resulted in a respective 20.9% and 3.8% decrease in BMD. Treatment with Sr had no significant effect to restore BMD in these skeletal sites. We observed a 15.4% decrease in vertebral bone compressive strength between control and binge alcohol treated rats. Sr co-treatment did not prevent this alcohol-induced decrease of bone strength. Analysis of serum osteocalcin levels demonstrated a 12.7% decrease in bone anabolism in binge alcohol treated animals. Sr co-treatment did not demonstrate a significant positive effect on this indicator of bone formation activity. Conclusions: While binge alcohol treatment resulted in measureable bone loss, SrCl treatment did not prevent these effects. This data suggests that Sr treatment, as performed in this protocol, is ineffective in preventing alcohol-induced bone loss. Perhaps higher doses of Sr, a formulation of the element other than SrCl, or a different mechanism of administration is needed to achieve a Sr level that can combat alcohol-induced osteopenia.

Poster 105
CANGRELOR (ARC69931MX) INCREASES HUMAN PLATELET cAMP LEVELS THROUGH AN ADP-P2Y12INDEPENDENT MECHANISM
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Background: ADP plays an integral role in the process of hemostasis by signaling through two platelet G protein-coupled receptors, P2Y1 and P2Y12. Based on the use of the adenosine-based P2Y12 antagonists such as ARC69931MX, which produce a broad spectrum of inhibitory activity against multiple platelet agonists, it is currently believed that ADP-P2Y12 pathway plays a central role in platelet activation. On the other hand, this general requirement for ADP-P2Y12 signaling in platelet activation seems to be inconsistent with earlier reports indicating that activation of certain platelet receptors can cause aggregation through ADP-independent mechanisms. Objective: Based on these apparent inconsistencies, we hypothesized that the broad spectrum of inhibitory activity displayed by ARC69931MX may derive from an elevation in platelet cAMP, which is known to produce general inhibition of platelet function. Methods: Platelet aggregation was analyzed in human platelet-rich plasma using turbidometric methods. cAMP analysis was performed by measuring the binding of 3[H]cAMP to protein kinase A. Results: It was found that the capacity of ARC69931MX to globally block platelet aggregation was dependent on its ability to significantly increase cAMP levels. Furthermore, it was also found that this elevation of cAMP did not require P2Y12-Gi signaling, or even P2Y12 receptors, but was mediated through a separate G protein-coupled pathway, presumably involving Gs. Further investigations revealed that ARC69931MX does not increase cAMP through activation of known platelet Gs coupled receptors, i.e., A2a, IP, DP or EP2. Collectively, these results show that ARC69931MX interacts with an unidentified platelet G protein-coupled receptor that stimulates substantial cAMP elevation and significant inhibition of platelet function. Conclusion: The present results identify a novel P2Y12-independent mechanism by which Cangrelor produces global inhibition of human platelet function. The significance of these findings derives from two considerations: 1. this reagent has been extensively used as a specific P2Y12 antagonist to identify ADP-P2Y12 signaling in many cell types; and 2. advanced clinical trials are currently evaluating Cangrelor as an antithrombotic agent based on a pharmacological mechanism that appears to be largely incorrect. On this basis, future studies will re-evaluate the contribution of ADP signaling to the process of human platelet activation both in vivo and in vitro.
Poster 106
POLYMER MICELLES WITH CROSS-LINKED IONIC CORES AS CARRIERS FOR ANTICANCER AGENT CISPLATIN
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Benefits of the frequently prescribed platinum (II) chemotherapy drug cisplatin are compromised by undesirable side effects, poor pharmacokinetics and development of drug resistance. Polymer micelles derived from amphiphilic block copolymers, offer a novel macromolecular platform for carrier based drug delivery, potentially overcoming such limitations. In this study, core cross-linked polymer micelles were evaluated as efficient carriers for the platinum (II) drug cisplatin. Structural modifications through changes in degree of cross-linking and nature of cross-linker were studied to allow slow and sustained release of the active drug. Poly(ethylene oxide)-poly(methacrylic acid) block copolymer (PEO-b-PMA) based core cross-linked micelles were synthesized via 1) condensation of PEO-b-PMA copolymers by Ca2+ into spherical micelles, 2) core cross-linking by using either 1,2-ethylenediamine or cystamine as cross-linkers and 3) removal of Ca2+ by extensive dialysis. Cisplatin was incorporated into the ionic core by reversible polymer-metal complex formation. The physicochemical properties, loading capacity and release kinetics were studied as a function of the degree of cross-linking of the ionic core, in either PBS (pH 7.4) or acetate buffer with saline (pH 5.5) at 37°C. Activity of the released drug was assessed by measuring its ability to affect the melting temperature (TM) of a model DNA oligonucleotide duplex and cytotoxicity against A2780 ovarian cancer cell line. Physicochemical analysis revealed a stable, nano-scale, narrowly dispersed micellar system, with a high loading capacity for cisplatin. The drug-carrier interaction was essentially reversible at physiological conditions allowing a sustained drug release profile in a pH responsive manner, with higher release rates at lower pH corresponding to the late endosomal pH. Cross-linking using cystamine allowed even faster drug release under reductive conditions, likely due to the cleavage of disulfide bonds in the ionic core. The released drug was found to decrease the TM of a model DNA oligonucleotide duplex indicating biologically relevant cisplatin-DNA covalent cross-links. The micelles loaded with cisplatin also retained cytotoxicity towards A2780 ovarian cancer cell line. In conclusion, stable core cross-linked polymer micelles can be utilized as efficient carriers for the platinum (II) drug cisplatin, allowing slow and sustained release of the drug without compromising its activity.

Poster 107
ROLE OF CORTISOLE IN ISCHEMIC PRECONDITIONING: NEW EVIDENCES
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Background: Ischemic preconditioning is a well known cardioprotective process. There are many endogenous peptides known responsible for this process. During the past two decades, many clinical studies found cardioprotective effects of corticosteroids, but their exact role in ischemic preconditioning remains questionable. Objectives: The aim of this study is to determine the role of cortisole in ischemic preconditioning. Methods: The experiments were 24 Male rabbits, divided randomly & equally to four groups: 1) sham, 2) Infarct, 3) Ischemic preconditioning (IP) and 4) Hydrocortisone (HYD). Hydrocortisone (50mg/kg) was injected 45min before major ischemia in HYD group. Serum levels of cardiac troponin-T(cTNT) and cortisole were measured before and after the protocols. Triphenyl-tetrazoliumchloride staining was done to determine the infarcted area (IA)and Area At Risk(AAR). Results: Among the IP and HYD groups, IA/AAR ratio was 18.29±6.48% and 7.68±1.99%, respectively in comparison to Infarct group (38.84±7.33%) (P<0.05). Serum levels of cortisole were increased from 3.39±0.79 ng/ml to 6.57±1.52 ng/ml and 47.91±15.52 ng/ml in Infarct and IP groups, respectively. An increasing trend in cortisole level was associated with a decreasing trend in infarct size and cTNT in the IP and HYD groups. Conclusion: In conclusion, we showed that hydrocortisone has cardioprotective effects when injected before the onset of myocardial infarction. In addition, we have proposed for the first time that endogenous hydrocortisone may play a role in ischemic preconditioning phenomena.Keywords: Hydrocortisone, Infarct size, Ischemia-reperfusion model, Ischemic preconditioning, serum cortisole.
The xeroderma pigmentosum complementation group C protein, encoded by the XPC gene, plays a key role in the nucleotide excision repair process. XPC is highly polymorphic, but only a few single nucleotide polymorphisms (SNPs) have been studied as potential modifiers of cancer risk. To date, the phenotypic effects of these SNPs have not been characterized, nor has their impact on DNA damage response and DNA repair capacity been determined. In this study, we constructed a comprehensive haplotype map encompassing the common SNPs in the XPC gene and evaluated their effect on DNA damage associated with smoking, using chromosome aberrations (CA) as a biomarker. We hypothesized that if certain haplotypes have phenotypic effects, there would be a correlation between these haplotypes and CA in smokers. Our results indicated that out of 92 SNPs identified, 35 had a minor allele frequency \( \geq 0.05 \). These 35 SNPs were used to construct a series of PHASE haplotypes in a standard population, and these haplotypes were then analyzed for phylogenetic relationships to create 6 distinct haplotype groups (phylogenetically grouped haplotype, or PGHs). Additionally, a haplotype-tagging (ht) approach was used to identify 11 htSNPs representing these 35 SNPs. We used these htSNPs to genotype a population of smokers matched to non-smokers (n=123), and used these genotypes to reconstruct haplotypes and assign appropriate haplotype groups for the study population. When we evaluated the relationship between these PGHs and CA, we observed that individuals with PGH-C had significant interaction between haplotype group and smoking status in terms of baseline CA frequency. We also observed significant interaction for PGH-D and near significant interaction for PGH-F between smoking status and PGH when cells were treated with an alkylating agent found in tobacco smoke. Given the strong association between CA and cancer, our data suggest that certain XPC haplotypes could significantly affect the risk of smoking-related cancers.