NATIONAL STUDENT RESEARCH FORUM

51st ANNUAL MEETING
April 22 – April 23, 2010

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

Supported by a grant from the
AMA Foundation
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The American Medical Association Foundation proudly sponsors the 2010 National and Regional Student Research Forums

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

**MEDICAL EDUCATION**

We encourage the best and brightest physicians-in-training through research seed grants and scholarships. Programs offer professional development opportunities and tuition assistance for medical school.

Kellie Rosinski, University of Washington and Fred Hutchinson Cancer Research Center, Seed Grant recipient

**PUBLIC HEALTH**

We fund educational initiatives and community service efforts across the country. Programs support free clinics that provide medical care to the uninsured, healthy lifestyles grants, and health literacy and patient safety resources.

The Clinic, Phoenixville, Pa., Healthy Communities/Healthy America grant recipient

To apply for research grants or scholarships, visit: www.amafoundation.org
Special Thank You to the 2010 National Student Research Forum Supporters

The awards presented at the 2010 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!

Department of Biochemistry and Molecular Biology
Department of Dermatology
Department of Neuroscience and Cell Biology
Department of Internal Medicine, Division of Cardiology
Department of Pathology
Department of Pediatrics
Department of Pharmacology and Toxicology
Department of Preventive Medicine and Community Health
Department of Orthopaedic Surgery and Rehabilitation
Department of Radiology
Department of Surgery
Department of Otolaryngology
Institute for the Medical Humanities
Institute for Human Infections and Immunity
School of Medicine, Office of Student Affairs and Admissions
Dear Forum Participants:

On behalf of the students, faculty and staff of The University of Texas Medical Branch, welcome to the 51st Annual National Student Research Forum. This wonderful tradition celebrates over 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.

This year’s speakers presenting at William C. Levin Hall are: Dr. Juri Gelovani, Professor, Chairman and Director of the Department of Experimental Diagnostic Imaging at MD Anderson will be giving a presentation on Experimental Molecular Imaging on Thursday, April 22nd from 12:00 to 1:00 p.m. Dr. Jonathan Ashwell, Chief of the Laboratory of Immune Cell Biology at the National Cancer Institute will deliver the Abreu Memorial Keynote Address that same date from 4:00 to 5:00 p.m. And on Friday, April 23rd at 1:30 p.m., Dr. Stefan Ambs, who leads the Breast and Prostate Cancer Unit at the National Cancer Institute, will present the Health Disparities Symposium Lecture.

Every year, we look forward with great anticipation to this event and hope you will take full advantage of the 2010 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 2010 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 fifty-first 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.
Sarah Hemauer
Senior 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 fourth year of the M.D./Ph.D. program. Her doctoral research in the Department of Biochemistry and Molecular Biology focuses on the role of the placenta in disposition of medications used to treat high risk pregnancies, and was awarded the Society of Maternal Fetal Medicine Award of Research Excellence in 2010. This is Sarah's third year co-directing the National Student Research Forum and first year as Senior Co-director.

Jill D'Souza
Co-Director

Jill D'Souza attended the University of St. Thomas, Houston, where she received her B.A. degree in Biology. Following graduation in 2007, she entered the UTMB School of Medicine and is now a 3rd year medical student. Jill plans to go on to residency in Otolaryngology/Head and Neck Surgery. Her current research focuses on referral and treatment patterns for common middle ear infections. This is Jill's first year serving as a Co-director for the National Student Research Forum.
John Anderson attended Kansas State University where he majored in Biology. He joined UTMB in 2006 and is now a 5th year MD/PhD student. John is performing his dissertation research in the laboratory of Jose M. Barral, M.D., Ph.D. at UTMB. His project involves understanding the mechanisms employed to accomplish protein folding and prevent misfolding in the healthy and disease state in the human brain. Since arriving at UTMB, John has been named a William D. and Jean C. Willis Research Scholar and a Truman Graves Blocker Junior Research Scholar. He has also won the GSBS Associates Award and the Seymour Fisher Award for Academic Excellence. Following medical school John plans to complete a residency and continue his research on understanding the process of protein folding and its relation to human disease. This is his first year as a Co-director for the National Student Research Forum.

Efrain Siller attended the University of Monterrey, Mexico where he obtained an MD degree. He joined UTMB in 2006 and is now a 4th year PhD student. His research in Jose M. Barral, M.D., Ph.D. laboratory focuses on the effects of ribosomal translation speed on protein folding efficiency. Efrain has been a Bromberg Scholar for the 2007-2008 and 2009-2010 periods. He won the Bohdan Nechay Tuition Scholarship Award in 2008. After graduate school, he plans to do a postdoc and continue his research on protein folding. This is his first year serving as a Co-director for the National Student Research Forum.
Latham Fink
Co-Director

Latham graduated from Rhodes College in 2003 with a B.S. in Mathematics and a B.A. in Philosophy. After leaving Rhodes, Latham researched the molecular genetics of muscle development at St. Jude Children’s Research Hospital. He then studied the role of viral RNA interference during infection and host immune evasion at UT-Austin. Latham is a second year medical student in the M.D./Ph.D. program and will soon begin his Ph.D. in the department of Pharmacology and Toxicology where he will conduct research on the epigenetics underlying addiction and drug abuse. Latham has presented his research at the International Conference of Polyomavirus and Human Disease. This is his first year serving as a Co-director for the National Student Research Forum.

Hilda Kriel
Co-Director

Hilda Kriel attended the University of Texas at Austin where she majored in Biomedical Engineering. While there, she did research in the synthesis of PLGA nanoparticles as well as the feasibility of separation of adipose-derived stem cells. She matriculated into UTMB in 2007 and is now a third year medical student. Hilda plans to do her residency in surgery after medical school. This is her first year serving as a Co-director for the National Student Research Forum.
Sydney Chun graduated summa cum laude from California State University Sacramento, where she majored in Molecular and Microbiology Biology with Honors in Research. She joined UTMB in 2008 and is a second year MD/PhD student. Her research interests lie in the field of infectious diseases, specifically pathogenesis, pathobiology, and pathogen-host interactions. She also has an interest in global health and tropical medicine, and in 2009 she was awarded a Fogarty International Research Fellowship to do research abroad in Lima, Peru. Sydney plans to go on to do her residency in Pediatrics or Internal Medicine Infectious Diseases after medical school, and continue her research in infectious diseases. This is her first year serving as a Co-director for the National Student Research Forum.
2010 Faculty Advisors

Maurice Willis, M.D.
Maurice Willis, MD is an Assistant Professor in the UTMB Department of Internal Medicine-Hematology/Oncology. He received his MD from Morehouse School of Medicine, Atlanta, GA. Dr. Willis serves as the UTMB Cancer Center Associate Director over the Clinical Enterprise, Co-director of the UTMB cancer center Multispecialty clinic, and Director of the UTMB and Texas Department of Criminal Justice Hematology/Oncology Clinics. His research interests include lung and prostate cancer.

Howard Brody, M.D./Ph.D.
Howard Brody (M.D., Michigan State University, 1976; Ph.D. in Philosophy, Michigan State University, 1977; residency in family practice, University of Virginia Medical Center, 1977-80), is the Director of the Institute for the Medical Humanities and John P. McGovern Centennial Chair in Family Medicine, University of Texas Medical Branch at Galveston.
Kristen Peek is an Associate Professor in the Division of Sociomedical Sciences Department of Preventive Medicine and Community Health and a Fellow at the Sealy Center on Aging at University of Texas Medical Branch (UTMB). She received her PhD in Sociology from Duke University in 1996 and then completed an NIA post-doctoral fellowship in the Department of Epidemiology at the University of Florida. Professor Peek’s research focuses on the effects of race and ethnicity on aging and physical and mental health. Since joining UTMB in 1998, she has conducted research on sociocultural processes affecting transitions into and out of disability among older Mexican Americans. In addition, she recently completed an R01 examining dyadic data on changes in spouses’ mental and physical health over time among older Mexican Americans. Currently, she is exploring the construct and predictive validity of allostatic load as a physiological marker of stress accumulated over the life course in a sample in Texas living near a petrochemical complex. Recent publications can be found in Social Science and Medicine, Journal of Epidemiology and Community Health, Journals of Gerontology, Annals of Epidemiology, and The Gerontologist.

Jose M. Barral, M.D./Ph.D.

Jose M. Barral, M.D./Ph.D. is an Assistant Professor in the Departments of Neuroscience and Cell Biology and Biochemistry and Molecular Biology, as well as the Sealy Center for Structural Biology and Molecular Biophysics. He received his MD from the Monterrey Institute of Technology and Higher Education, Monterrey, Mexico, 1995, his PhD at Baylor College of Medicine, Houston, Texas, 2001. His research interests include human diseases are known to result, directly or indirectly, from aberrant protein folding reactions. A major area of research in his laboratory is to study proteins with similarities to molecular chaperones that, when mutated, lead to neurodegenerative disorders.
David W. Niesel, Ph.D.

David W. Niesel, Ph.D., is the Chair and Professor of the UTMB Department of Microbiology and Immunology. He also serves as a Member of the Center for Tropical Medicine and Sealy Center for Structural Biology, Senior Member of, Sealy Center for Vaccine Development, and Vice Dean of the UTMB Graduate School of Biomedical Sciences. Dr Niesel received his Ph.D. from North Carolina State University. Dr. Niesel’s laboratory is investigating in vivo models of gene/protein expression by the respiratory pathogen Streptococcus pneumoniae and facultative intracellular bacteria. In addition, his research group is investigating alterations in gene/protein expression and alterations to the virulence potential of S. pneumoniae in a low shear environment. He has had multiple experiments performed on the space shuttle and on the International Space Station. The Niesel lab is also interested in the initial responses of host cells to bacterial pathogens, which lead to new initiation of cellular signaling and the host immune response.
2010 Senior Faculty Advisor

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).
2010 51st National Student Research Forum
Schedule of Events

WEDNESDAY, April 21, 2010

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 22, 2010

7:30 am – 4:00 pm  Registration Table Open
                   Foyer – Levin Hall

7:30 am – 9:00 am  Continental Breakfast
                   Foyer – Levin Hall

8:30 am – 9:00 am  Welcome Address
                   Levin Hall Main Auditorium

9:00 am – 10:15 am Oral Session A: Biochemistry and Cell Biology
                   Levin Hall:  3.320

                   Oral Session B: Microbiology and Immunology
                   Levin Hall:  3.324

                   Oral Session C: Neuroscience
                   Levin Hall:  South Auditorium

10:15 am – 10:30 am Break

10:30 am – 12:00 pm Oral Session A – continued
                   Levin Hall:  3.320

                   Oral Session B - continued
                   Levin Hall:  3.324

                   Oral Session C - continued
                   Levin Hall:  South Auditorium

12:00 pm – 1:00 pm Lunch Seminar
                   Experimental Molecular Imaging
                   Dawid Schellingerhout, M.D.
                   Levin Hall Dining Room
1:00 pm – 3:00 pm  Poster Session 1
Levin Hall Foyer

4:00 pm – 5:00 pm  Abreu Keynote Memorial Lecture:
Jonathan Ashwell, M.D.
Levin Hall Main Auditorium

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

**FRIDAY, April 23, 2010**

8:00 am – 4:00 pm  Registration
Foyer – Levin Hall

8:00 am – 9:00 am  Continental Breakfast
Foyer – Levin Hall

9:00 am – 10:15 am  Oral Session D: Oncology and Cancer Biology
Levin Hall:  3.320

Oral Session E: Pathology
Levin Hall:  3.324

Oral Session F: Surgery and Orthopedic Medicine
Levin Hall: South Auditorium

10:00 am – 12:00 pm  Poster Session 2
Levin Hall Foyer

10:15 am – 10:30 am  Break

10:30 am – 12:00 pm  Oral Session D - continued
Levin Hall:  3.320

Oral Session E - continued
Levin Hall:  3.324

Oral Session F - continued
Levin Hall: South Auditorium

12:00 pm – 1:30 pm  Bench to Bedside Lunch
Featuring: The Institute for Translational Sciences
Levin Hall Dining Room
1:30 pm – 3:30 pm  Health Disparities Symposium:
Lecture: Stefan Ambs, Ph.D, M.P.H.
Levin Hall: South Auditorium
Focus Groups
Levin Hall: 3.320, 3.324, South Auditorium, Dining Room

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

8:00 pm – 10:00 pm  After Party
Poolside
Hilton Galveston Island Resort
IN APPRECIATION

The 2010 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 NSRF.
- 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 NSRF.
- 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 NSRF.
- Drs. José M. Barral, Howard Brody, M. Kristen Peek, David W. Niesel, and Maurice Willis, the 2010 National Student Research Forum Faculty Advisors, for their commitment, guidance, and dedication to the Forum.
- Drs. Allan Brasier and the Institute for Translational Sciences, for their aid in making the Bench to Bedside lunch possible.
- Dr. John D. Prochaska, Meredith Masel, David Beasley, D. Mark Estes, Martin G. Myers, Bruce Luxon, Michele Carter, David W. Niesel, and Norbert K. Herzog for their assistance in Coordinating the focus groups for the Health Disparities Symposium.
- Glenda McKinney, for her advocacy of the Forum and proofreading help of many manuscripts.
- Drs. Jonathan Ashwell, Stefan Ambs, and Juri Gelovani 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 dedicated work, there would be no Forum.
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.

UTMB Faculty
Sherif Abdel-Rahman, Ph.D.
Mahmoud Ahmed, Ph.D.
Ashraf Aly, MD Ph.D.
Sheryl Bishop, Ph.D.
Paul Boor, M.D.
Nigel Bourne, Ph.D.
William Buford, Ph.D.
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Larry Denner, Ph.D.
Miriam Falzon, Ph.D.
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Evelyn McKinney, Ph.D.
Terumi Midoro-Horiuti, M.D./Ph.D.
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Pomila Singh, Ph.D.

Kizhake Soman, Ph.D.
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Giulio Taglialetela, Ph.D.
Tracy Toliver-Kinsky, Ph.D.
Gustavo Valbuena, M.D./Ph.D.
Tushar Varma, Ph.D.
John Wiktorowicz, Ph.D.
Maurice Willis, M.D.

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Michelle Barton, Ph.D.
Paul Chiao, Ph.D.
Diane Chico, Ph.D.
Rod Fabian, M.D.
Donald Frohlich, Ph.D.
Winifred Hamilton, Ph.D.
Heidi Hofer, Ph.D.
Ben Jansen, Ph.D.
Brian Knoll, Ph.D.
John Ladbury, Ph.D.
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Gary Shaw, Dr.P.H.
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Xiaobing Shi, Ph.D.
Giulio Taglialetela, Ph.D.
Tracy Toliver-Kinsky, Ph.D.
Randall Urban, M.D.
Yi Wang, Ph.D.
Jue Wang, Ph.D.
William Willis, M.D.
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 presentations 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 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 Oral Presentation in Pathology
Best Oral Presentation in Surgery and Orthopedic Medicine

Best Poster Presentation in Biochemistry and Cell Biology
Best Poster Presentation in Cardiology
Best Poster Presentation in Dermatology
Best Poster Presentation in Genetics
Best Poster Presentation in Humanities and Social Sciences
Best Poster Presentation in Microbiology and Immunology
Best Poster Presentation in Public Health
Best Poster Presentation in Radiology
Best Poster Presentation in Neuroscience
Best Poster Presentation in Oncology
Best Poster Presentation in Pharmacology and Toxicology
Best Poster Presentation in Surgery and Orthopedic Medicine
The Oslerian Award for Translational Research
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.
Jonathan Ashwell, M.D.

Dr. Ashwell received his M.D. from Columbia University College of Physicians and Surgeons. He completed a residency in internal medicine at Presbyterian Hospital in New York City. Following a postdoctoral fellowship in immunology in the laboratory of Dr. Ronald Schwartz (National Institute of Allergy and Infectious Diseases/NIH), Dr. Ashwell joined the NCI as a principal investigator. He was named Chief of the Laboratory of Immune Cell Biology in 1992.

Dr. Ashwell’s research interests include signaling molecules, mechanisms and biological relevance of apoptosis. Signaling via the T cell receptor results in a large number of biochemical and biological outcomes: tyrosine kinase activation, cytokine production, proliferation, and apoptosis. Apoptosis is a means of eliminating unwanted cells. Many cells, including immature and mature lymphocytes, undergo apoptosis under the appropriate conditions. Inappropriate apoptosis has clearly been shown to result in both tumor formation and autoimmunity (lack of appropriate cell death) and has been implicated in the loss of CD4+ cells in AIDS (death of functionally useful cells). He is interested in examining the mechanisms and biological relevance of apoptosis in a number of settings.

IAP (Inhibitor of Apoptosis) proteins constitute a family of molecules that have roles in regulating signaling pathways and can, in fact, have pro-apoptotic activity. He is currently studying how IAP activity is regulated in cells, and what effect loss of IAP expression has in knockout animal models.

Several molecules and signaling pathways involved in T cell function and development are also under investigation: p38, a MAP kinase (MAPK) involved in inflammatory processes; GADD45a, a small adaptor protein involved in p38 and JNK activation; and IL-7, a cytokine found in the thymus and peripheral lymphoid organs that has anti-apoptotic and pro-proliferative activities.
Dr. Stefan Ambs is a tenure-track investigator at the National Cancer Institute (NCI), Bethesda, MD, and head of the Breast and Prostate Cancer Unit, Laboratory of Human Carcinogenesis, Center for Cancer Research. He received his Master's degree in Biochemistry from the University of Tübingen (1988) and completed his Ph.D. at the Institute of Toxicology, University of Würzburg, Germany (1992). He also earned a Master of Public Health degree (Epidemiology) from Johns Hopkins Bloomberg School of Public Health (2005). Dr. Ambs was trained in translational research as a Postdoctoral Fellow at the NCI under the mentorship of Dr. Curtis C. Harris (1992-1997). He continued his research at a biotechnology company in California and at the Aventis Genomics Center in Cambridge, Massachusetts. In 2001, he returned to the NCI as an investigator in the field of Molecular Epidemiology.

Dr. Ambs and his colleagues conduct molecular epidemiology studies of breast and prostate cancer with an emphasis on health disparity and utilize epidemiological and translational research strategies to identify risk factors for tumor development and progression. Their research links tumor markers to cancer epidemiology and seeks to identify causal principles and mechanisms in experimental settings. He is the principal investigator of a large case-control study of prostate cancer that is in the recruitment phase and will examine risk factors for the disease among African-American and European-American men in the greater Baltimore area. His group is also collecting tumor tissue from both breast and prostate cancer patients with an epidemiological profile for further molecular investigations. His breast cancer research is exploring the influence of inflammation and common genetic variations on tumor characteristics and survival, and is examining gene expression profiles and their relationship to inflammatory breast cancer and to differences in tumor biology between African-American and European-American patients. Recent research has focused more on prostate cancer and led to the discovery of tumor immunobiological differences between African-American and European-American patients and a diagnostic microRNA signature in collaboration with Dr. Carlo Croce. Future research will continue to evaluate the relative contribution of tumor biology to the existing survival health disparities between African-American and European-American prostate and breast cancer patients.
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 20 of this program.
A - 1  Bland, Christopher S.  
9:15  Baylor College of Medicine  
REGULATION OF ALTERNATIVE RNA SPlicing DURING MYOGENIC DIFFERENTIATION

A - 2  Jordan, Stephen J.  
9:30  University of Alabama at Birmingham  
IDENTIFICATION OF A NOVEL MALARIA VACCINE: CROSS-REACTIVE ANTIBODIES IN A HYPOENDEMIC SETTING

A - 3  Kotecha, Ritesh R.  
9:45  Albany Medical College  
ASSESSING THE ROLE OF DCAF11 IN HIV-1 Vpr MEDIATED G2 CELL CYCLE ARREST

A - 4  Krisman, Smitha  
10:00  University of Texas Medical Branch  
INTRACELLULAR BAX TRAFFICKING: A DETERMINANT OF CELL DEATH

A - 5  Madani, Mohammad H.  
10:30  LSU Health Sciences Center  
IN VolVEMENT OF RAC GTPASE IN EPAC-MEDIATED ENDO THELIAL BARRIER PROTECTION

A - 6  Shenaq, Deana S.  
10:45  The University of Chicago Pritzker School of Medicine  
THE DIFFERENTIAL EFFECTS OF BMP-2 AND BMP-9 IN MURINE CALVARIAL DEFECTS
B - 1  Hackett, Daniel J.
9:15  University of Alabama at Birmingham School of Medicine
AN ELISA METHOD FOR CYTOMEGALOVIRUS GLYCOPROTEIN B ANTIBODY MEASUREMENT IN SERUM

B - 2  Jackson, Stephanie R.
9:30  Saint Louis University School of Medicine
OVERCOMING T CELL TOLERANCE TO PROVIDE DURABLE ADOPTIVE IMMUNOTHERAPY OF CANCER

B - 3  Tai, Wendy M.
9:45  Baylor College of Medicine
MULTI-STRAIN INFLUENZA PROTECTION INDUCED BY A LIPOSOMAL MUCOSAL IMMUNOTHERAPEUTIC

B - 4  Valdis, Matthew
10:00  Schulich School of Medicine and Dentistry at the University of Western Ontario
MESENCHYMAL STEM CELLS INDUCE IMMUNE TOLERANCE THROUGH THE GENERATION OF REGULATORY T-CELLS; A POTENTIAL THERAPY FOR CELL MEDIATED AUTOIMMUNE DISEASE
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<td>Al Bulushi, Yarab M.</td>
<td>College of Medicine &amp; Health Sciences, Sultan Qaboos University, Oman</td>
<td>SERUM PROLACTIN LEVELS IN MIGRAINE</td>
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<td>C - 2</td>
<td>Attenhofer, Kevin S.</td>
<td>Louisiana State University Health Sciences Center in New Orleans, LA</td>
<td>ASSESSMENT OF OCULOMOTOR PERFORMANCE IN THE PARKINSONIAN PATIENT</td>
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<td>C - 3</td>
<td>Datta, Proleta</td>
<td>Graduate School of Biomedical Sciences, University of Texas at Houston</td>
<td>SYNAPTIC VESICLE POOLS ASSOCIATED WITH SNARE COMPLEXES IN RETINAL BIPOLAR NEURONS</td>
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<td>C - 4</td>
<td>Halabi, Anasheh</td>
<td>Louisiana State University School of Medicine at New Orleans, LA</td>
<td>AMYLOID BETA PEPTIDE PERTURBS CELL FUNCTION THROUGH EARLY TARGETING OF MITOCHONDRIA</td>
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<td>C - 5</td>
<td>Molina, Miguel F.</td>
<td>Louisiana State University Health Science Center</td>
<td>THE NOVEL PRO-APOPTOTIC HIGH MOBILITY GROUP BOX 1 (HMGB1) MODULATES NEUROPROTECTIN D1-MEDIATED CELL SURVIVAL SIGNALING</td>
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<td>C - 6</td>
<td>Watkins, Stacey M.</td>
<td>University of Alabama School of Medicine</td>
<td>BIOPHYSICAL AND BIOMECHANICAL ASPECTS OF GLIOMA INVASION</td>
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51st Annual NSRF
Oncology and Cancer Biology
Oral Session D
Friday, April 23, 2010
9:00am
Levin Hall 3.320

D - 1  Chen, Kevin S.
9:15 Duke University School of Medicine
CYTOMEGALOVIRUS ANTIGENS AS AN IMMUNOTHERAPEUTIC TARGET FOR ADVANCED GLIOMAS

D - 2  Cheung, Eleanor
9:30 Robert Wood Johnson Medical School
BREAST AWARENESS AND BREAST SELF-EXAMINATION IN CANCER DIAGNOSIS OF HIGH-RISK WOMEN

D - 3  Martinez, Danielle R.
9:45 Baylor College of Medicine
CHARACTERIZATION OF A NOVEL MITOSIS-ASSOCIATED HISTONE MODIFICATION

D - 4  Rastergar, Farbod
10:00 University of Chicago- Pritzker School of Medicine
LYSOPHOSPHATIDIC ACID ACYLTRANSFERASE-BETA AND ITS ROLE IN OSTEOSARCOMA

D - 5  Sethi, Nilay S.
10:30 UMDNJ - Robert Wood Johnson Medical School (M.D.) and Princeton University (Ph.D.)
TUMOR-DERIVED JAGGED1 PROMOTES OSTEOLYTIC BONE METASTASIS OF BREAST CANCER BY ACTIVATING STROMAL NOTCH SIGNALING

D - 6  Sud, Maneesh
10:45 University of Manitoba
UP-REGULATION OF THE MTOR AND PROTEASOME PATHWAYS IN EVI1+ ACUTE MYELOID LEUKEMIAS
51st Annual NSRF
Pathology
Oral Session E
Friday, April 23, 2010
9:00am
Levin Hall 3.324

E - 1  Davis, Rachael
9:15  Loyola University Chicago Stritch School of Medicine
BIOCHIP ARRAY PROFILING OF INFLAMMATORY MARKERS IN END STAGE RENAL DISEASE

E - 2  O'Connor, Michael
9:30  Indiana University School of Medicine
ASPARTATE AMINOTRANSFERASE (AST) TO PLATELET RATIO INDEX (APRI) PREDICTS LIVER FIBROSIS PROGRESSION IN PARENTERAL NUTRITION-DEPENDENT INFANTS LESS THAN 1-YEAR OF AGE

E - 3  Rahman, Saudur
9:45  Loyola University Stritch School of Medicine
ELEVATED LEVELS OF CIRCULATING MICROPARTICLES IN DISSEMINATED INTRAVASCULAR COAGULATION AND THEIR IMPACT ON INFLAMMATORY PROCESS

E - 4  Raza, Sajjad
10:00  Dow University of Health Sciences, Karachi, Pakistan
VARIATIONS IN PRESENTATION OF CELIAC DISEASE IN ADULTS AND ITS ASSOCIATION WITH OTHER CONDITIONS

E - 5  Starr, Marlene
10:15  University of Texas Medical Branch
VULNERABILITY TO SEPSIS IN THE AGED IS LINKED TO REDUCED PROTEIN C PATHWAY ACTIVATION
51st Annual NSRF
Surgery and Orthopedic Medicine
Oral Session F
Friday, April 23, 2010
9:00am
Levin Hall South

F - 1  Carness, Jeffrey M.
9:15  University of Texas Medical Branch
FLUID RESUSCITATION USING INTRAOSSEOUS VASCULAR ACCESS: FLOW RATES WITH LACTATED RINGER’S AND HETASTARCH

F - 2  Chokshi, Aalap
9:30  Columbia University College of Physicians and Surgeons
HEPATIC DYSFUNCTION AND MELD SCORES IMPROVE AFTER ORTHOTOPIC HEART TRANSPLANTATION AND PREDICT POST-TRANSPLANTATION MORTALITY

F - 3  Kamel, Sarah H.
9:45  Indiana University School of Medicine
THE ROLE OF LAPAROSCOPIC EVALUATION TO DETECT A CONTRALATERAL DEFECT AT INITIAL PRESENTATION FOR INGUINAL HERNIA REPAIR

F - 4  Miller, Daniel J.
10:00  Columbia University College of Physicians and Surgeons
ELECTRONIC MONITORING IMPROVES BRACE WEARING COMPLIANCE IN PATIENTS WITH ADOLESCENT IDIOPATHIC SCOLIOSIS

F - 5  Raj, Sean D.
10:30  New York University School of Medicine
SHOULD ENDOVASCULAR REPAIR BE OFFERED TO AORTIC ABDOMINAL ANEURYSM PATIENTS WITH SHORT INFRARENAL NECKS

F - 6  Yu, Yangyang R.
10:45  University of Cincinnati College of Medicine
COMPLICATIONS OF LOW-PROFILE DORSAL VERSUS VOLAR LOCKING PLATES IN THE DISTAL RADIUS: A COMPARATIVE STUDY
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 20 of this program.
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<td>Chokshi, Aalap</td>
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<td>VENTRICULAR ASSIST DEVICE IMPLANTATION REVERSES IMPAIRED MYOCARDIAL METABOLISM AND LIPOTOXICITY IN ADVANCED HEART FAILURE</td>
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<td>Colish, Jane M.</td>
<td>University of Manitoba</td>
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<td>OBSTRUCTIVE SLEEP APNEA: EFFECTS OF CONTINUOUS POSITIVE AIRWAY PRESSURE ON CARDIAC REMODELING AS ASSESSED BY CARDIAC BIOMARKERS, ECHOCARDIOGRAPHY AND CARDIAC MRI</td>
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<td>Shah, Kevin</td>
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<td>INCREASED 90-DAY MORTALITY IN ACUTE HEART FAILURE PATIENTS WITH ELEVATED COPEPTIN LEVELS</td>
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<td>Sheikh, Muhammad A.</td>
<td>Dow Medical College, Dow University of Health Sciences, Karachi, Pakistan</td>
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<td>IDENTIFICATION OF CARDIOMETABOLIC RISK IN MEDICAL STUDENTS</td>
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<td>Tadin, David M.</td>
<td>Louisiana State University Health Sciences Center in New Orleans, LA</td>
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<td>CARDIAC REMODELING IS WORSENED BY CIGARETTE SMOKE</td>
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<td>Vu, Eric</td>
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<td>FORTILIN AUGMENTS ATHEROSCLEROSIS FORMATION IN A HYPERLIPIDEMIC TRANSGENIC MOUSE MODEL</td>
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<td>Antony, Ashley</td>
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<td><strong>Fang, Daniel Z.</strong></td>
<td><em>University of California, San Diego</em></td>
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<td><strong>Gonzales, Andrea K.</strong></td>
<td><em>Universidad Nuestra Señora De La Paz; La Paz-Bolivia</em></td>
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<td><strong>Kaur, Mandeep</strong></td>
<td><em>The University of Texas – Austin</em></td>
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<td><strong>Nauman, Feryal</strong></td>
<td><em>Dow Medical College, Dow University of Health &amp; Sciences, Karachi, Pakistan</em></td>
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<td><strong>Obayan, Busayo K.</strong></td>
<td><em>Boston University School of Medicine</em></td>
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<td><strong>Zardouz, Shawn</strong></td>
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<td>Al Dhahli, Ahmed</td>
<td>Sultan Qaboos University, College of Medicine and Heath Sciences</td>
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<td>Harris, Tara J.</td>
<td>The George Washington University School of Medicine</td>
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<td>Ochoa, Kelly</td>
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<td>Weissman, Jacqueline R.</td>
<td>Cleveland Clinic Lerner College of Medicine of Case Western Reserve University</td>
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*West Virginia University School of Medicine*  
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28  Mercer, Joel Z.  
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29  Mrachek, Edward Kelly  
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34 Crisman, Celina M.  
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35 Hussain, Fawwad Ahmed  
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REGULATION OF ALTERNATIVE RNA SPLICING DURING MYOGENIC DIFFERENTIATION

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Background- Most transcripts in metazoans are alternatively spliced. The majority of known disease-causing mutations are predicted to alter pre-mRNA splicing, implicating splicing misregulation as a major cause of human disease. Furthermore, splicing misregulation is widely believed to act as the major pathogenic mechanism in a number of diseases, including Myotonic Dystrophy (DM). However, little is known about the regulation of alternative splicing (AS) during development. We have used the C2C12 mouse myogenic cell line as a model to study AS regulation during cellular differentiation.

Objective- We sought to identify conserved, regulated transitions in AS that occur during C2C12 differentiation, identify the determinative regulatory motifs, and assess the role of AS in differentiation.

Methods- We used splicing sensitive microarrays to identify AS events during C2C12 differentiation, which were all confirmed by RT-PCR. Biocomputational analysis was used to identify motifs associated with regulated alternative exons. Implicated AS regulators were depleted from C2C12 cells using lentiviral mediated shRNA, and resulting differentiation phenotypes were characterized by Western blot, immunofluorescence, and phase-contrasted microscopy.

Results- We identified over 100 confirmed myogenic AS transitions. We examined orthologous exons during quail myoblast differentiation and found that many AS transitions are conserved. Motifs associated with the AS regulatory protein Rbm9 are significantly enriched and conserved within the intronic regions surrounding regulated alternative exons. C2C12 cells depleted of Rbm9 showed dramatic morphological defects of differentiation, including a substantial decrease in myotube formation, despite normal upregulation of differentiation markers.

Conclusions- The data demonstrates that AS regulation is highly conserved during myogenic differentiation and that the AS regulatory factor Rbm9 is required for normal myogenic differentiation. We intend to further characterize the differentiation defects associated with Rbm9 depletion and examine the roles of other putative splicing regulators during myogenic differentiation.

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IDENTIFICATION OF A NOVEL MALARIA VACCINE: CROSS-REACTIVE ANTIBODIES IN A HYPOENDEMIC SETTING.

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Plasmodium falciparum Merozoite Surface Protein 3 (PfMSP3) is a strong candidate for inclusion in a blood stage vaccine cocktail. Like many merozoite surface proteins, PfMSP3 is polymorphic and vaccine development to date has focused largely on the C-terminal domain, which is more conserved. However, field data suggests that the PfMSP3 N-terminus is much more immunogenic than the C-terminus, and antibodies against the N-terminal domain can correlate with protection from severe malaria. Given that the PfMSP3 N-terminus is polymorphic, it will only be useful as a vaccine target if cross-reactive antibodies can be generated to provide protection against different antigenic variants. To establish whether such cross-reactive antibodies develop in vivo, we have conducted a systematic study of antibody dynamics generated against each PfMSP3 domain in individuals living in a malaria-hypoendemic environment in the Peruvian Amazon.

ELISA assays were carried out using two different PfMSP3 N-terminal antigens, based on the currently circulating genotypes present at the study site, as well as a PfMSP3 C-terminal antigen conserved in both alleles. Given the low transmission dynamics (less than one infection per person per year), individuals are usually infected with clonal P. falciparum infections spaced many months apart. All the infection samples used in the study have been previously genotyped for PfMSP3 allele and sequence diversity, allowing us to compare the immune response against both the currently infecting PfMSP3 antigen sequence and a PfMSP3 antigen that the individual has not been exposed to for at least one year. By measuring the strength and isotype profile of antibody responses against each antigen, we have found that there is a level of cross-reactivity between PfMSP3 N-terminal alleles that is equivalent to the reactivity against the PfMSP3 C-terminal antigen and supports the development of a novel N-terminal based PfMSP3 vaccine.
The HIV/AIDS epidemic currently remains a significant global health burden, affecting approximately 33 million individuals worldwide. In the search for innovative therapeutic interventions, viral proteins have been intensely studied for future treatments that disrupt key host/viral protein interactions in order to block successful viral replication and infection. Both the human immunodeficiency virus type 1 and type 2 (HIV1/HIV2) encode a conserved viral protein, Vpr, which plays an important role during HIV infection by triggering G2 cell cycle arrest in dividing cells, and facilitating infection of non-dividing cells. To cause G2 cell cycle arrest, Vpr engages a host DDB1•Cul4 ubiquitin ligase complex through the adaptor protein DCAF1, thereby recruiting specific host proteins for ubiquitination. An analysis of proteins that assemble with Vpr may reveal other host proteins that function in this degradation pathway as well. The present study focuses on DCAF11, a DDB1•Cul4 associated factor that has been previously reported to associate with DDB1 directly, which we found to also physically interact with HIV1 Vpr. To further characterize the interactions between DCAF11 and the complex formed by HIV1 Vpr and the ubiquitin ligase, we designed a series of co-immunoprecipitation experiments in HEK293T cells. Our preliminary data show that DCAF11 is degraded in the presence of HIV1 Vpr, but not HIV2 Vpr or HIV2 Vpx. Furthermore, we show that HIV1 Vpr causes the ubiquitination and subsequent degradation of DCAF11 through the host DCAF1•DDB1•Cul4 ubiquitin ligase complex in a dose dependent manner. Consistent with previous studies, we have also confirmed that DCAF11 directly binds to DDB1, and we further show that DCAF11 directly binds to HIV1 Vpr as well. Our data also suggests a role for DCAF11 in HIV1 Vpr function, as we show that overexpression of DCAF11 is able to inhibit HIV1 Vpr mediated G2 cell cycle arrest. Taken together, these results identify a novel target for HIV1 Vpr-mediated degradation, and set the stage for investigating the role of this host/viral protein interaction in HIV1 infection.

Background: Brain damage due to neonatal hypoxia-ischemia (HI) is a major cause of morbidity and mortality in infants. Objective: Our long-term goal is to characterize HI-induced intracellular localization of Bax in order to develop intervention strategies that may prevent permanent damage in the developing brain of infants. Methods: Here we measured Bax multi-organelle localization after in vivo HI-injury and after 100% O2 resuscitation and its correlation with organelle-specific cell death signaling. In addition to examining HI- and HHI- treated cortical Bax protein, we used rotenone-treated P5 neuronal cortical cultures, differentiated PC12 and SY5Y cells to better characterize the role of Bax shuttling in cell death signaling cascades. In particular, we examined the role of Bax phosphorylation after apoptotic and necrotic-like cell death stimuli. We asked whether HI-dependent differential phosphorylation of Thr167 and Ser163 residues determines Bax intracellular localization. Results: Neonatal (P7) brain HI induces intracellular translocation of Bax to the nucleus, mitochondria, and ER, where it triggers activation of cell death signaling cascades. When compared to HI-treated rat pups, we found that 100% O2 resuscitation of HI-treated (HHI) rat pups increases HI-induced ER Bax levels, ER-mediated cell death signaling, and lesion volume likely due to an increase in necrotic-like cell death, triggering an over-activation of inflammatory signaling. We also observed an increase in p-BaxThr167 in the nucleus of cortical tissue at 1 hour after HI when compared to shams. Conclusions: This suggests a role for phosphorylation in the translocation of Bax to the nucleus. Understanding the mechanisms of Bax translocation will aid in the rational design of specified therapeutic strategies which could potentially involve altering Bax subcellular redistribution to decrease the irreversible trauma resulting from a prolonged inflammatory response.
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IN INVOLVEMENT OF RAC GTPASE IN EPAC-MEDIATED ENDOTHELIAL BARRIER PROTECTION
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Endothelial cells have a key role in barrier function of the vasculature. Impaired endothelial barrier integrity can lead to deleterious outcomes such as massive edema. Vascular permeability is associated with cardiovascular disease, sepsis, trauma, cancer metastasis, and diabetes. Cyclic AMP (cAMP) and Protein kinase A (PKA) dependent pathways have been previously shown to enhance endothelial cell barrier integrity. An additional pathway activated by cAMP involving the guanine exchange factor Epac and its downstream target, Rap1 GTPase also promotes enhanced endothelial barrier function. We tested the hypotheses that 1) Epac promotes enhanced endothelial barrier function via Rac-1 signaling, and 2) during thrombin-induced endothelial barrier dysfunction, selective Epac activation can rescue barrier function. We used human umbilical vein endothelial cells (HUVEC) grown on small gold electrodes to measure transendothelial electrical resistance (TER), an indicator of barrier function. 8-CPT-2'-O-Me-cAMP (200 µM) was used to specifically activate Epac without affecting PKA. To block Rac1, we used NSC-23766 (200 µM), a cell permeable pyrimidine compound that specifically inhibits the interaction between Rac1 and Tiam1. Rac1 activation was determined with an ELISA kit that measures Rac1-GTP concentrations. The results show that 8-CPT-2'-O-Me-cAMP caused a marked increase in TER. Blockade of Rac1 activity with NSC-23766 reduced TER, and also inhibited 8-CPT-2'-O-Me-cAMP-induced barrier enhancement. In addition, 8-CPT-2'-O-Me-cAMP treatment for 5 minutes increased Rac1-GTP levels in HUVEC compared to untreated controls. 8-CPT-2'-O-Me-cAMP pretreatment significantly inhibited thrombin (1 U/ml)-induced barrier dysfunction. When 8-CPT-2'-O-Me-cAMP was added 5 minutes after the initiation of thrombin-induced barrier dysfunction, TER increased rapidly toward baseline levels, and barrier function was restored much more quickly than in HUVEC with thrombin alone. These results suggest that the Epac-Rap1 pathway may serve as a potential therapeutic strategy for resolving excessive microvascular leakage.

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THE DIFFERENTIAL EFFECTS OF BMP-2 AND BMP-9 IN MURINE CALVARIAL DEFECTS
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Background: Bone Morphogenic Proteins (BMPs) play a pivotal role in bony regeneration and differentiation. Our previous data showed that BMP-9 generates one of the most robust osteogenic responses. Currently, only BMP-2 and 7 are FDA approved for clinical use, and limited information is available about the osteogenic capability of other BMPs. Objective: We aim to assess the osteogenic effects of BMP-9 and BMP-2 in an in vivo mouse model of critical sized calvarial defects. Methods: Non-suture associated 4mm parietal defects were created in adult CD1 male mice (age ≥8 weeks, n=19). Adenoviral vectors encoding BMP-9 (n=6), BMP-2 (n=5), or GFP alone (control, n=5) were impregnated into collagen sponges, filling the defects (0.5 x 106 pfu/defect). One group (n=3) was treated with collagen sponge alone. MicroCT scans of live subjects permitted serial defect survey (3, 6, 12, 16-weeks post craniotomy). Using Amira software (Amira 5.2.1, Mercury Computer Systems, San Diego, CA), defect closure and bony maturation were assessed by creating 3D volumetric renderings at a threshold of 400 Hounsfield units, depicting defect intensity. Calvaria were harvested at 20 weeks and de novo osseous regeneration was assessed by histology. Results: MicroCT imaging showed increased bony regeneration in adBMP-9 and adBMP-2 groups by week 3. AdBMP-9 had a significant percent change in defect intensity from baseline (240.0%±65.0%) vs adGFP controls (63.0%±26%) by 6 weeks (p=0.04), whereas, a significant change was seen by 16 weeks in the adBMP-2 group (336.7%±194.0% vs 72.0%±25.9%, p=0.03). The adBMP-9, adBMP-2, and adGFP groups all had significantly greater intensity changes than the sponge only control (p<0.05). No significant difference was seen between the adBMP groups at any timepoint. Conclusion: We have established a reliable and reproducible model of critical-sized murine calvarial defects. Here, BMP-2 and BMP-9 are potent osteogenic agents. Further studies should be performed to evaluate the potential clinical utility of BMP-9, and to comprehensively test the differing regenerative effects of BMPs in the craniofacial skeleton.
AN ELISA METHOD FOR CYTOMEGALOVIRUS GLYCOPROTEIN B ANTIBODY MEASUREMENT IN SERUM
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Background: Cytomegalovirus (CMV) is the leading cause of congenital infection in developed countries and an important opportunistic pathogen in immunocompromised patients. Measurement of antibody to CMV glycoprotein B (gB), a highly immunogenic envelope glycoprotein, is valuable in assessment of antibody response to infection and to CMV gB vaccines. Objective: To create an assay and method of calculating endpoint dilution that can measure serum antibody response to CMV gB in those with naturally acquired infection and both uninfected and infected vaccine recipients in a CMV gB vaccine clinical trial. Methods: An ELISA method with a purified, recombinant CMV gB molecule as antigen was evaluated. Sera from 168 CMV IgG positive and 100 seronegative subjects were used to evaluate the assay. A cut-off optical density (OD) value was to distinguish gB antibody positive from negative sera. Antibody titers to gB determined by endpoint dilution were compared with those calculated using regression analysis. Run to run and inter-operator reproducibility of results were measured. Results: The mean OD + 5 standard deviations from 50 CMV IgG antibody negative sera (0.2472) was used as the cut-off between gB antibody positive and negative. All sera from 100 CMV IgG seronegative subjects were negative for antibody to gB. Over 99% of seropositive subjects tested were positive for gB antibody. Observed antibody levels based on titration to endpoint were very similar to results calculated using linear regression. Run to run consistency of endpoints was excellent with 38 runs from one operator and 48 runs from another all giving results within one dilution of the mean value for each of three CMV IgG antibody positive serum pools. Conclusions: This assay gives accurate and reproducible results for the quantity of CMV gB IgG in serum over a wide range of antibody levels and distinguishes sera that are positive or negative for CMV antibody nearly as well as a whole virus antigen assays. The fact that over 99% of CMV antibody positive subjects tested had antibody to gB provides further evidence that the gB antigen contains highly conserved immunogenic domains that are recognized by antibodies stimulated by infection by all CMV strains. Future studies will include: 1) Evaluating the assay using a larger sample size in order to determine whether this assay could be used to screen patients for past CMV infection; 2) Adapting this assay for measurement of CMV gB IgG antibody avidity.

OVERCOMING T CELL TOLERANCE TO PROVIDE DURABLE ADOPTIVE IMMUNOTHERAPY OF CANCER
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One of the primary challenges to effective adoptive T cell immunotherapy for cancer is the induction of tolerance in transferred T cells upon encounter with tumor, as many tumor antigens are aberrantly or over-expressed self-antigens. Our previous results revealed that expression of a second T cell receptor (TCR) provided a mechanism by which tolerance could be overcome via immunization through this second receptor, but such an approach has not yet been evaluated as a therapeutic intervention of established disease. Our current work examines tolerance induction in dual-TCR (dTCR) T cells transferred into mice (Alb:Gag) that express a tolerizing self-antigen (Gag) in the liver, which is also expressed as a tumor antigen in FBL leukemia. Immunization of tolerant Gag-specific dTCR T cells through a second expressed receptor (specific for Gp33) rescued T cell function in vivo, and thus represents a potential new strategy to improve immunotherapy against progressive and disseminated cancer. To evaluate this potential, we transferred CD8+ dTCR T cells into either normal B6 mice or Alb:Gag recipients (in the absence or presence of tolerizing Gag self-antigen). Analysis of blood at 4 days and spleen at 12 days post-transfer revealed 50% and 86% reductions, respectively, in the percentage of dTCR T cells in Alb:Gag vs. B6 mice, suggesting that most of the transferred Gag-reactive T cells are deleted after encounter with peripheral Gag self-antigen. To determine if the few remaining dTCR T cells had become tolerant, recipient mice were immunized by infection with an attenuated ActA-deficient Listeria monocytogenes (Lm) bacteria strain engineered to express Gag or Gp33 antigen. Responses were examined 7 days post-immunization, and showed anticipated deletion of dTCR T cells in the presence of self-antigen. Immunization of B6 recipients with Lm-Gag resulted in a 6-fold expansion of dTCR T cells. However, no expansion of dTCR T cells was observed in Alb:Gag mice, demonstrating a profound tolerogenic phenotype to the Gag antigen. In contrast, dTCR T cells were induced to proliferate and expand in response to stimulation through the second receptor with Lm-Gp33 immunization, even within the tolerizing Alb:Gag environment. These data demonstrate that expansion of tolerant dual-TCR T cells is achievable by immunization through a second TCR and suggest similar strategies may result in rescue of tolerant T cells with implications for adoptive immunotherapy of cancer.
Background: Bivalent influenza virus (INFV) A vaccines composed of purified HA and NA surface proteins are widely used for protection against INFV pneumonia, but require annual reformulation and only incompletely protect vulnerable patient subsets. We have developed a novel T cell-based vaccine that obviates most limitations of current vaccines. Our non-viable trivalent vaccine is comprised of short, highly conserved peptides derived from M2, HA, and NP formulated with the TLR ligands (TLRLs), monophosphoryl lipid A (MPL) and trehalose dimycolate (TDM) in a dilauroylphosphatidylcholine (DLPC) multilamellar liposome matrix. Objective: We hypothesize that intranasal immunization with short, conserved, and immunogenic peptides will confer universal protection to lethally infected mice. Methods: The tri-peptide vaccine (TPV) was administered IN as a liposomal emulsion (50 μl) to 4-6 weeks old C57Bl/6 mice on d-21, -14, and -7 prior to INFV A and B infection (d0). Additional animals received only lipid vehicle. All animals were infected on d0 with LD90 INFV A/HK or B/Lee via aerosol. Survival, weight loss, and symptom scores were monitored for 20d post infection. Lung viral burden, ELISPOT assays, and flow cytometric analysis were performed. For long-term memory studies, mice were infected at 60d or 90d post treatment. Mice that received IN boosters were infected 7d post treatment. Lungs were assessed for histopathological changes and for NP tetramer-positive CD8 T cells. Results: PAS staining of lung sections showed reduced inflammation and mucus secretion associated with TPV treatment. 100% survival and minimal change in both weight and symptom scores were observed relative to mice that received vehicle. Although TPV treatments did not persist past 8 wks, it was able to confer partial protection to mice that received an IN booster (40% survival). Staining of lung cells demonstrated ≥17.6% NP+ CD8+ T cells after administration of IN booster. Furthermore, NP peptide reactive cells produce IFN-γ. Mechanistically, protection was achieved by enhancing viral clearance. As early as d2 after infection with INFV A/HK, viral replication was reduced by 2 log in the lungs of TPV treated vs. vehicle treated mice. Conclusion: Our findings indicate that although T cells play an important role in viral clearance, additional booster treatments are necessary to extend long term protection.

MESENCHYMAL STEM CELLS INDUCE IMMUNE TOLERANCE THROUGH THE GENERATION OF REGULATORY T-CELLS; A POTENTIAL THERAPY FOR CELL MEDIATED AUTOIMMUNE DISEASE

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Background: Mesenchymal Stem Cells (MSCs) have been shown to suppress proliferation of CD4+ T-cells in vitro. This immunosuppressive property has been extensively studied, but remains controversial. Recent evidence has shown that T-regulatory cells (T-regs), which express CD25 (IL-2 receptor) and the Forkhead Box p3 (FOXP3) protein, may contribute to this property. The eventual use of mesenchymal stem cells as an immunosuppressive therapy hinges on the elucidation of this mechanism. Objective: To identify the mechanism of MSCs immunosuppression and then use unmatched human MSCs to induce immune suppression in the treatment of immune-competent Streptozotocin (STZ) induced diabetic mice. Methods: Flow cytometry analysis of CD4+ cells was used to monitor changes in expression of T-regs induced by human umbilical cord-blood derived MSCs. The contribution of these cells to immune suppression was then verified with FOXP3 siRNA inhibition as well as with a FOXP3 inhibitory anti-body. After this mechanism was verified, thirty-six C57BL/6 mice were given IP injections of STZ for 5 days to induce hyperglycemia. This led to a drastic increase in blood glucose concentrations after 15 days, at which point mice were treated with 10⁶ human MSCs. These mice were monitored for a reduction in blood glucose levels, and blood samples were taken at days 1, 15 and 21 to monitor the levels of circulating insulin in MSC treated mice as compared to the non-treatment group. Results: Flow cytometry of cell cultures indicated an increase in the expression of CD4+CD25Bright+FOXP3+ cells from 0.08% to 0.62%, of all CD4+ cells when MSCs are present during mixed lymphocyte reactions. Transfection of these cells with both FOXP3 siRNA as well as FOXP3 antibody ameliorated the effects of the MSCs, increasing proliferation back to the levels seen with the non-transfected controls. MSC treatment altered blood glucose and insulin levels compared to control groups. Fluorescent microscopy of tissues showed that transplanted human MSCs avoid immune recognition in immune competent unmatched hosts and preferentially migrate to sites of inflammation (pancreas and spleen) where they can be recovered in high concentrations. Conclusions: This research shows that MSCs suppress proliferation of T-cells through the formation of CD25Bright+FOXP3+ T-Regs and clearly demonstrates the great potential these cells hold in the development of new therapeutic strategies for T-cell mediated autoimmune diseases.
Background and Objectives: The hypothalamic involvement in chronic migraine has been previously studied and a decrease in nocturnal prolactin peak was found. It was hypothesized that there is a sustained nocturnal inhibition of prolactin by dopamine secretion. Prolactin is an essential hormone for lactation that is synthesized in the anterior lobe of the pituitary gland. It has been associated with the pathogenesis of migraine and considered one of its aggravating factors. This study aims to investigate the relationship between serum prolactin level and various types and stages of migraine.

Methodology: Twenty-three patients with migraine (mean age, 29.8 ±10.2 years; range, 12 to 50 years; 4 males, 19 females) and seven healthy subjects (mean age, 27.6 ±12.3 years; range, 12 to 47 years; 3 males, 4 females) were studied. Serum prolactin level was estimated according to the general guidelines of Jeffcoate et al. using “Coat-A-Count Prolactin IRMA” kit.

Results: Compared to the control group, serum Prolactin levels were significantly high in Migraine group as a whole (P value <0.05) and during the attacks (P <0.05). It was particularly high in the group without aura collectively (P <0.04) and during attacks (P <0.03).

Discussion: This study demonstrated significantly high mean baseline serum prolactin levels in Migraine group (both sexes) compared to controls (P<0.05). A recent study has found a significant association between high serum prolactin levels and worsening of migraine symptoms. Other studies reported either normal or low levels. The results of these studies were not statistically significant and their contradicting results could be attributed to the difference in the composition of study samples and the presence of many factors which may interfere with proper serum prolactin estimation. In concordance with previous studies, serum prolactin levels in female patients did not differ during and in between attacks (P >0.1).

Conclusion: Basal serum prolactin levels in migraine are abnormal indicating a latent prolactin disturbance which may play a role in migraine pathogenesis.

ASSESSMENT OF OCULOMOTOR PERFORMANCE IN THE PARKINSONIAN PATIENT

Parkinson’s disease (PD) is a progressive, neuro-degenerative disease that affects the body’s motor functions by damaging the extrapyramidal dopaminergic system. The primary symptoms include rigidity, tremor at rest, bradykinesia, and postural instability. These disruptions in motor performance affect patients in many ways, including limiting their eye movements. While many studies have been conducted to document oculomotor control in PD subjects, they are most often testing highly controlled laboratory tasks that do not accurately represent real-life situations. In this study, the eye movements of PD and control populations were examined while performing a designed prosaccade/antisaccade task as well as during a free image viewing scenario (a slideshow) which attempts to reflect real-life situations. As patients were viewing these predetermined sets of images, the movement of their eyes was measured by a SensoMotoric Instruments’ iView X™ Hi-Speed 1250 and then analyzed in SensoMotoric Instruments’ BeGaze, Microsoft Excel 2007, and MathWorks’ MatLab. The prosaccade/antisaccade task was used to assess the interrelationships between various areas of the Parkinsonian brain by manipulating a reflexive response. The slideshow task was used to evaluate the affects of PD on free eye movement. Using the control group as a baseline for normal, it was found that PD patients have longer latency times during the prosaccade/antisaccade task and a higher rate of direction errors. This indicates that PD patients respond slower to stimuli and when they do, they are less able to overcome prepotent reflexes, as supported by the tonic inhibition model. Interestingly, PD subjects’ saccades and fixations did not differ greatly from that of the control population during the slideshow task, suggesting that the effects of PD on the extraocular muscles are limited.
SYNAPTIC VESICLE POOLS ASSOCIATED WITH SNARE COMPLEXES IN RETINAL BIPOLAR NEURONS
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Background: Retinal bipolar neurons form ribbon-style synapses, characterized by organelles called "synaptic ribbons" which tether synaptic vesicles at active zones. Neurotransmitter release occurs via SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complex-mediated exocytosis. In bipolar neurons, three kinetic components of release have been described that are attributed to the fusion of vesicles that are docked and ribbon-associated (the rapidly-releasing pool; RRP), followed by the recruitment and fusion of other ribbon-associated vesicles (the releasable pool; RP), followed by reserve vesicles from the cytoplasm. Objective: To better understand the functional organization of vesicle pools at a ribbon synapse, we asked which release components are sensitive to a SNARE-competing peptide. Methods: Membrane capacitance and calcium current were monitored in isolated goldfish bipolar cell terminals. Terminals were dialyzed with a peptide derived from the N-terminal part of the SNARE domain of goldfish syntaxin 3B (synt3B) via the patch pipette. A scrambled peptide served as control. A stimulus train designed to capture the three components of release was given every 60s. Results: One minute after break-in, terminals dialyzed with synt3B peptide exhibited a decrease in the total extent of exocytosis evoked by the train compared to controls. Closer examination of terminals dialyzed with the synt3B peptide revealed that the first two components (RRP and RP) of release were intact, while the third (reserve pool) was inhibited (p<0.05). With subsequent trains, there was progressive decrease in the first two components of release in terminals dialyzed with synt3B peptide relative to controls. These changes were not due to a decrease in calcium current. By the third stimulus train, 180s after break-in, the RRP and RP were significantly reduced relative to controls (p<0.002). However, when the first stimulus was given at 180s, there was no decrease in the size of the RRP and RP, indicating that the block by the synt3B peptide required activity-dependent vesicle turnover. Conclusions: In contrast to vesicles in the reserve pool, vesicles in both the RRP and RP are initially resistant to the synt3B peptide. However, the SNARE-competing peptide inhibits exocytosis from these two pools in an activity-dependent manner. Thus vesicles in the ribbon-associated pool have preformed SNARE complexes.

AMYLOID BETA PEPTIDE PERTURBS CELL FUNCTION THROUGH EARLY TARGETING OF MITOCHONDRIA
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BACKGROUND: Alzheimer's disease (AD) is a progressive, neurodegenerative disorder that results in cognitive decline. AD pathology includes accumulation of the peptide amyloid β (Aβ) that aggregates as amyloid plaques as well as somatodendritic hyperphosphorylation of tau forming neurofibrillary tangles. Similarly, in age-related macular degeneration (AMD), Aβ aggregates are found in drusen and correlate with retinal pigment epithelial (RPE) cell and photoreceptor degeneration. OBJECTIVE: Our hypothesis is that Aβ(1-42) targets RPE cell mitochondria impairing cell survival and function. METHODS: A protocol was standardized for the conversion of synthetic, monomeric Aβ(1-42) into the toxic, oligomeric form found in both AD and AMD. We used the human RPE cell line, ARPE-19, and conditioned medium with oligomeric Aβ(1-42) to assess cell viability. Cell viability was studied by: a) chromatin condensation using Hoechst staining as a marker of apoptosis, b) LDH assays as indicators of necrotic cell death and c) mitochondrial viability using MTT assays. Confocal microscopy was then utilized to determine the effects of Aβ(1-42) on mitochondrial structure. RESULTS: Hoechst staining and the LDH assay indicated that Aβ(1-42) induces 1% cell death in ARPE-19 cells. However, MTT assays show time-dependent, toxic activity of Aβ(1-42) on the mitochondrial oxidation-reduction potential reducing it to 35% below normal. Confocal microscopy with the mitochondrial marker Rhodamine 1,2,3 and Alexa-Fluor®488 labeled-amyloid in addition to a MitoTracker, illustrate the damage mediated by Aβ(1-42) on the mitochondria. CONCLUSIONS: These experiments demonstrate that Aβ(1-42) mediates mitochondrial damage in RPE cells. This data can be used to help define the cell signaling that underlies changes in mitochondrial integrity and its significance in the early pathology of AMD and AD. Future studies will refine imaging techniques using electron microscopy and establish whether or not mitochondrial fragmentation occurs. In addition, the application of anti-inflammatory agents can be tested to determine if mitochondrial depolarization can be halted or delayed. In doing so, potential therapeutic strategies can be developed against AMD and AD.
THE NOVEL PRO-APOPTOTIC HIGH MOBILITY GROUP BOX 1 (HMGB1) MODULATES NEUROPROTECTIN D1-MEDIATED CELL SURVIVAL SIGNALING.
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Oxidative stress triggers apoptosis in RPE cells. An early rescue response is the enzymatic production of neuroprotectin D1 (NPD1) that down-regulates the expression of pro-inflammatory signaling and enhances the expression of anti-apoptotic proteins. We hypothesize that NPD1 signaling modulates gene expression engaged in the homeostatic survival response. To construct the NPD1-transcriptome, enrichment analysis was used to identify the over-represented genes for common, similar and unique sets. Functional ontologies, Gene Go and GO cellular processes were applied. More than 300 genes were shown to be modulated in response to NPD1. The transcription factor network analysis showed the involvement of HNF4-alpha, NF kB, c Jun and EGR1 among others. Together the data was plotted in a network map showing NPD1-mediated modulated genes and proteins showing HMGB1 as a key factor in the regulation. HMGB1 is a versatile protein that is involved in ligand activity binding RAGE receptors and in the co-activation of gene expression. We propose that HMGB1 is a novel factor in NPD1 survival signaling. To test this prediction, RPE with stable silenced 15-LOX-1 and normal cells were transfected with plasmids containing 4 different shRNA targeting HGMB1. Plasmid number 1 showed 50% silencing in cultures where the transfection efficiency reached 60%. Oxidative stress induced apoptosis was highly decreased by the silencing of HMGB1 in normal cells but did not affect 15-LOX-1 knocked down cells. Immunocytochemistry showed a cytoplasmic but not nuclear localization of HMGB1 in ARPE-19 after 8 hours of treatment, not being appreciable any translocation at that time point. All together these results suggest that HGMB1 is a negative regulator of NPD1 signaling upon oxidative stress stimulation.

BIOPHYSICAL AND BIOMECHANICAL ASPECTS OF GLIOMA INVASION
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Malignant gliomas are among the deadliest cancers with very limited treatment options. Diffuse invasion into the surrounding brain makes surgical resection challenging. Invading cells encounter tortuous extracellular spaces necessitating profound changes in cell shape and presumably cell volume. However, whether and how cell regulate shape and volume is poorly understood. Hence the main objective of this study was to examine specific biophysical and biochemical changes that permit glioma cells to journey through the confines of the brain. Based on prior findings we hypothesize that cell volume decreases as cells invade and that this is due to the release of Cl- and K+ along with obligated water. To examine this hypothesis we established an ex-vivo invasion model that mimicked the spatial constraints of glioma invasion while allowing us to image the process in real time. Specifically, we used a Transwell assay system in which GFP-tagged glioma cells were challenged to traverse through 8.0 µm pores from one compartment to another while being imaged in a climate controlled chamber using a laser scanning confocal microscope. Image stacks were acquired at various time points of the migration sequence, allowed 3D volume reconstruction and accurate volume measurements. To examine whether the cell nucleus also underwent volume alterations, a nuclear dye was loaded into GFP-tagged cells prior to migration experiments to create simultaneous image stacks to determine nuclear volume changes. Data obtained thus far indicated that the total cell volume decreased on average by 32% while the nuclear volume decreased 52% until the cell have traversed the barrier. In addition we imaged the migration of glioma cells along blood vessels in brain slices either after seeding on top or implanting tumors in vivo. These studies also showed a 33% and 29% reduction of cell volume, respectively. Current efforts are focused on imaging glioma invasion in vivo through multi-photon imaging through a cranial window. To establish a causal relationship between cell volume changes and ion fluxes, inducible shRNA constructs have bee developed for the candidate genes to selectively disrupt ion release. These studies will allow to examine the requirement for volume changes in gliomas with the potential to develop future anti-invasive therapies.
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CYTOMEGALOVIRUS ANTIGENS AS AN IMMUNOTHERAPEUTIC TARGET FOR ADVANCED GLIOMAS
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Background: Even with standard-of-care surgery, radiation and temozolomide (TMZ) chemotherapy, median survival for patients with glioblastoma multiforme (GBM) remains less than 15 months. Immunotherapy targeting tumor-specific antigens is an attractive option since it combines specificity with strong anti-tumor efficacy. Recent data from our lab and others have shown expression of cytomegalovirus (CMV) antigen in greater than 90% of GBMs, without expression of these antigens in surrounding normal brain. Thus, CMV epitopes may be ideal targets in GBM immunotherapy. Furthermore, although one might suspect TMZ treatment to have a detrimental effect on vaccine-based approaches to immunotherapy, we have shown that vaccine response may actually be increased during TMZ-induced lymphodepletion. The generation of a CMV-specific response can thus be harnessed and translated toward anti-GBM therapy. Objective: To elicit potent CMV specific immune responses during recovery from TMZ chemotherapy-induced lymphodepletion in a mouse model of human immunity. Methods: Transgenic mice expressing human HLA-A2.1 were vaccinated i.d. with three weekly vaccines using HLA-A2.1 restricted peptide sequences of CMV proteins pp65 or IE1, or with a mixture of 15mer polypeptides spanning the sequence of pp65 or IE1 (peptide mix). Vaccines consisted of 100µg peptide with 800 U/mL GM-CSF emulsified with Freund’s complete or incomplete adjuvant. Lymphocytes isolated from lymph nodes and spleens were stimulated with either HLA-A2.1 specific peptide or non-specific peptide. Immune response was measured by levels of cytokine at 72 hours using a cytometric bead array. Results: Vaccination with pp65 peptide mix demonstrated IFN. responses in draining lymph nodes (p<0.05) and splenocytes (p<0.001). Moderate TNFa and IL-2 responses were also observed. Immune response to IE1 immunization is under evaluation. Conclusions: Feasibility of engendering immune response to CMV peptide vaccine has been shown in HLA-A2.1 transgenic mice. Subsequent studies will investigate the impact of TMZ-induced lymphodepletion on these responses and resultant anti-tumor efficacy using a CMV-associated astrocytoma model.

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BREAST AWARENESS AND BREAST SELF-EXAMINATION IN CANCER DIAGNOSIS OF HIGH-RISK WOMEN
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BACKGROUND: The value of breast self-examination (BSE) has been called into question in recent years. However, selected clinical recommendations and some evidence still advocate monthly BSE in high-risk women, suggesting that new cancers may be diagnosed via BSE even with concurrent yearly mammography and breast MRI. OBJECTIVE: To determine the percentage of breast cancers diagnosed via breast awareness. Also, to determine the rates of breast self-examination among high-risk women, and factors that influence performance of BSE. METHODS: We surveyed 1084 women at high risk of hereditary breast cancer who underwent genetic counseling and BRCA testing over the last 12 years at two sites. Our comprehensive survey queried high-risk women about screening practices and, if applicable, their diagnosis of breast cancer. Statistical analyses included descriptive, comparative, and multivariate regression analyses. RESULTS: 684 women reported a diagnosis of breast cancer and described its detection. 49% (336) reported their breast cancer was first detected when they personally felt a lump. 36% (245) reported cancer detected on mammography screen, and 9% (60) reported that a doctor or nurse first felt a lump. To examine BSE practice, we excluded participants with bilateral mastectomies, providing a cohort of 876 women with an average age of 52. 37% (325) reported performing BSE according to current recommendations for high-risk women, at least once per month. 16% (138) reported never performing BSE. The remaining 47% (413) reported performing BSE 1-6 times per year. On multivariate analysis, likelihood of performing monthly BSE was increased with a history of breast cancer (odds ratio [OR]=1.8, 95% confidence interval [CI]=1.4,2.4). BSE performance decreased with increasing socioeconomic status (OR=0.9, 95% CI=0.8, 0.99). In this preliminary analysis, age, BRCA status, race, and other screening practices had no effect on the likelihood of performing monthly BSE. CONCLUSIONS: In this cohort of high-risk women, nearly half of breast cancer cases were diagnosed due to the patient herself feeling a lump, despite the debated value of BSE. Women with a history of breast cancer or a lower socioeconomic status were more likely to perform monthly BSE. Important next steps include discovery of other factors that affect performance of BSE, and prospective trials examining the effectiveness of BSE in diagnosing breast cancer in high-risk women.
CHARACTERIZATION OF A NOVEL MITOSIS-ASSOCIATED HISTONE MODIFICATION
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The nucleosome is the fundamental unit of chromatin; it consists of an octamer of histones proteins (H3, H4, H2A and H2B units) around which DNA is wrapped. The N-terminal tails of Histone H3 and H4 are the targets of many histone-modifying enzymes. The consequences of these modifications vary greatly and are important for various cellular activities, including mitosis. Lysine residues on histone H3 can mono-, di-, or trimethylated (me1, me2, and me3, respectively), with most of the H3 methylation marks occur on the histone N-terminal tail. However, H3 methylation can also occur on lysine 79 (H3K79), which is an exposed residue on the histone fold motif of histone H3. Adjacent to H3K79 is threonine 80 (H3 T80), which is a potential phosphorylation mark, and like H3 K79 is conserved on all histone H3 isoforms. The current study focuses on a novel histone modification involving the trimethylation of K79 and simultaneous phosphorylation of T80 (H3 K79me3/pT80). We initially became interested in H3 K79me3/pT80 because we observed that H3 K79me3/pT80 immunoreactivity is only evident in proliferating cells, and is undetectable in senescent or quiescent cells. Using flow cytometry and immunofluorescence analysis, we have determined that K79me3/pT80 is a cell cycle-associated histone modification appearing during late G2 and peaking during mitosis. We have also found that K79me3/pT80 is associated with all regions of the condensed chromosomes during mitosis. In addition, H3 K79me3/pT80 completely co-localizes with Histone H3 phosphorylated on serine 10 (H3 pS10), a well-known mitosis marker, suggesting that both modifications may be regulated in the same fashion. However, H3 K79me3/pT80 occurs on an exposed region of the histone core, meaning that it is not removed by proteolytic cleavage of histone H3's N-terminus. To determine the relevance of H3 K79me3/pT80 in vivo, immunohistochemistry (IHC) was used to examine H3 K79me3/pT80 in primary human melanoma tumors. Interestingly, we were able to observe mitotic cells via H3 K79me3/pT80 IHC in primary melanoma tumors. Since mitotic cells in vivo can be detected via K79me3/pT80 IHC, H3 K79me3/pT80 may prove to be a beneficial diagnostic tool for diagnosing and determining the invasiveness of human melanoma. Currently mutagenesis analysis is being used to examine the role of H3 K79me3/pT80 in mitosis, and to understand the mechanism of H3 K79me3/pT80 regulation.

LYSOPHOSPHATIDIC ACID ACYLTRANSFERASE-BETA AND ITS ROLE IN OSTEOSARCOMA
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Background: Lysosphosphatidic acid acyltransferase beta (LPAAT-B) is an enzyme involved in lipid biosynthesis whose role in tumor progression has been emerging in the last few years. The product of its enzymatic reaction phosphatidic acid (PA) is an important component of mammalian target of rapamycin (mTOR) a well defined signaling cascade in osteosarcoma the most common primary malignancy of the bone. Objective: In this study we will explore the role of LPAAT-B in osteosarcoma growth and proliferation. Methods: LPAAT-B expression was determined by RT-PCR. Exogenous expression or knockdown of LPAAT-B was mediated utilizing adenoviral vector delivery. Cell proliferation and migration was measured in-vitro. The in-vivo tumor formation was assessed by xenograft studies. Results: We investigated the expression level of LPAAT-B in 10 different osteosarcoma lines using semiquantitative RT-PCR and demonstrated a proportional increase in LPAAT-B expression in cell lines with more malignant phenotype. Using adenoviral mediated knockdown of LPAAT-B we illustrated significant reduction in osteosarcoma proliferation measured quantitatively using MTT assay and qualitatively using crystal violet staining. Tumor migration was measured using wound healing assay showing a decrease in migration of adenoviral mediated knockdown group compared to control. We identified the role of LPAAT-B on tumor growth in-vivo using murine xenograft model and our results show significant reduction in tumor growth of the group transfected by LPAAT-B knockdown compared to the control (p< 0.05). Conclusion: Our findings provide evidence that, LPAAT-B expression level is directly correlated with tumor growth in osteosarcoma lines providing a possible new therapeutic approach to managing osteosarcoma.
TUMOR-DERIVED JAGGED1 PROMOTES OSTEOLYTIC BONE METASTASIS OF BREAST CANCER BY ACTIVATING STROMAL NOTCH SIGNALING

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Background: The Notch pathway is essential for proper embryonic development and is increasingly being recognized for its role in stem cell regulation and pathogenesis of cancer. Despite evidence supporting an oncogenic role in breast cancer, the mechanism underlying the pathway's contribution to metastasis remains unknown. Objective: Investigate the clinical, functional, and mechanistic importance of the Notch pathway ligand Jagged1 in promoting osteolytic bone metastasis and evaluate the efficacy of a gamma secretase inhibitor (GSI) as therapy against bone metastasis. Methods: We employ a xenograft in vivo mouse model to test the ability of genetically modified human tumor cells to metastasize to the bone using real-time bioluminescent imaging and histopathological analysis. This model is also extended for preclinical testing of therapeutic agents such as GSIs. We compliment results from in vivo studies with staining of human breast cancer tissue specimens for clinical significance and an in vitro mammalian co-culture system for mechanistic insight. Results: We report that elevated expression of the Notch pathway ligand Jagged1 in breast cancer is associated with aggressive metastatic ability and an increased incidence of bone metastasis in patients. Immunohistochemical staining of clinical patient samples revealed that Jagged1 is overexpressed in the basal-like subtype of breast cancer. Functional studies in mice revealed that tumor-derived Jagged1 promotes osteolytic bone metastasis by activating Notch signaling in the supporting bone stromal components. Jagged1-overexpressing tumor cells acquire a growth advantage in the bone microenvironment by stimulating IL-6 release from associated osteoblasts in a Notch-dependent manner. Furthermore, tumor-derived Jagged1 directly activates osteoclast differentiation, giving rise to a severe osteolytic bone phenotype. Importantly, GSI treatment reverses Jagged1-mediated bone metastasis by disrupting the Notch pathway in bone stromal cells. Conclusions: Our results shift the paradigm for Notch signaling in breast cancer, as we define a requirement for the pathway in the supporting stroma of bone metastases rather than the tumor cells. We provide evidence supporting Jagged1-Notch signaling as a clinically and functionally important mediator of tumor-stroma interactions that supports osteolytic bone lesions and provides rationale for the use of GSIs as a potential therapy against bone metastasis.

UP-REGULATION OF THE MTOR AND PROTEASOME PATHWAYS IN EVI1+ ACUTE MYELOID LEUKEMIAS

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Introduction: Acute myeloid leukemia (AML) is a group of hematological malignancies of which the defining features are aberrant gene expression patterns caused by genetic abnormalities. A subset of AML patients over-express the EVI1 (ectopic viral integration 1) transcription factor oncogene that resides at 3q26. The clinical outcome of EVI1+ patients is poor with conventional chemotherapy. This suggests that the identification of transcriptome features unique to EVI1+ patients may explain this resistance and provide a path to improved therapy. Methods: We used a microarray-based gene expression approach to characterize the signatures associated with EVI1+ positivity in tissue samples from the Princess Margaret Hospital Leukemia Tissue Bank. RNA prepared from the peripheral blood blast samples of AML patients was reverse-transcribed, labelled and hybridized to Agilent Human Whole Genome Expression Arrays. Statistical analyses were carried out with Gene Set Enrichment Analysis Software (GSEA). Results were validated using quantitative RT-PCR. A high throughput MTS-based screening assay for drug sensitivity was used to determine the in vitro drug susceptibility of an EVI1+ cell line. Results: We identified 10 patients with 3q26 abnormalities over-expressing EVI1 (3q26+/EVI1+), 4 patients without 3q26 abnormalities over-expressing EVI1 (3q26-/EVI1+) and 12 patients with neither 3q26 abnormalities nor EVI1 expression (3q26-/EVI1-). Kaplan-Meier survival analysis demonstrated a reduction in overall survival for 3q26+ patients (N=10) when compared to 3q26- patients (N=16, P=0.0326). GSEA revealed genes within the mTOR and Proteasome pathways were up-regulated in EVI1+ patients relative to EVI1- patients. Results were confirmed by qRT-PCR. Lastly, a cell line (OCI-AML14) derived from an EVI1+ patient was susceptible to in vitro treatment with an mTOR inhibitor, rapamycin. Conclusions: EVI1+ AML is associated with several activated pathways, namely mTOR and Proteasome, for which inhibitors are available and already in clinical use.
BIOCHIP ARRAY PROFILING OF INFLAMMATORY MARKERS IN END STAGE RENAL DISEASE

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End Stage Renal Disease (ESRD) presents a complex syndrome in which systemic vascular pathophysiologic changes contribute to adverse cardiovascular and cerebrovascular manifestations. Inflammatory and hemostatic aberrations contribute to the overall pathogenesis of the syndrome. The purpose of this study is to profile inflammatory mediators which will provide useful data on the pathogenesis and underlying mechanism of vascular comorbidities in ESRD. Plasma samples from 51 patients with ESRD were collected during maintenance hemodialysis sessions. A group of ten normal individuals, both male and female, were included as control. Cerebral Array II chips were used in the Randox® system to simultaneously measure Neuron Specific Enolase (NSE), Neutrophil Gelatinase-associated Lipocalin (NGAL), Soluble Tumor Necrosis Factor Receptor I (TNFRI), D-Dimer (DD), Thrombomodulin (TM), and C-reactive protein (CRP). The Randox® Evidence Investigator™ is a new biochip array technology that utilizes multiple discrete test regions of immobilized antibody to simultaneously quantify multiple markers from a single patient plasma sample based on the light signal generated from each test region. As compared to the normal individual, all of the markers studied showed an upregulation in patients with ESRD. Most notably TNFRI showed a 25 fold increase in patients with ESRD (mean 7.4 ± 2.4, range 3.1 to 13.6) compared to the control (mean 0.3 ± 0.1, range 0.2 to 0.5). TM showed a 6.6 fold increase (mean 7.0 ± 2.5, range 2.5 to 14.1) compared to control (mean 1.1 ± 0.2, range 0.8 to 1.4), and NGAL showed a 5.5 fold increase (mean 1416 ± 203, range 839 to 1729), compared to control (mean 257 ± 74, range 115 to 377). Increases in CRP and DD were also noted up to 2.8 fold. Although NSE showed a trend toward a 1.2 fold upregulation, this result was not statistically significant. The elevation of TNFRI suggests a state of increased cellular damage. Similarly, the increase in the other markers of inflammation indicates a polypathologic process which may predispose ESRD patients to both cardiovascular and cerebrovascular thromboembolic events. Also, this study further validates the role of endothelial damage and endogenous thrombotic processes in ESRD as evidenced by the increased levels of TM and DD. These studies show that some newer markers such as TNFRI, NAGAL and NSE are increased in ESRD. However, the clinical significance of these markers still needs to be further explored.

ASPARTATE AMINOTRANSFERASE (AST) TO PLATELET RATIO INDEX (APRI) PREDICTS LIVER FIBROSIS PROGRESSION IN PARENTERAL NUTRITION-DEPENDENT INFANTS LESS THAN 1-YEAR OF AGE

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Background: Infants with parenteral nutrition (PN) dependence may develop cholestatic liver dysfunction. The aspartate aminotransferase (AST) to platelet ratio index (APRI) has good correlation with liver fibrosis progression in adults and in infants with short gut. Objective: This study applies APRI scoring to PN-dependent short gut infants to determine hepatic fibrosis progression in relation to estimated gestational age (EGA), age at resection, and intestinal length. Methods: Laboratory values and liver biopsies were collected from initiation of PN for a period of 26 weeks. Fibrosis scoring ranged from F0 (normal) to F4 (cirrhosis). For each EGA, age at resection, and intestinal length, children were analyzed. All patients required some intestinal resection, and all were less than two months (0-58 days, 12.6 days) of age at initiation of PN. Median APRI by fibrosis grade was F ≤ 2: 1.87, F3: 5.71, and F4: 14.74 (p<0.01). Average post-resection APRI progression over time stratified by EGA, age at resection, and intestinal length showed three distinct periods. From 0-8 weeks post-PN initiation, little difference was seen in APRI scores among the groups in all three stratifications. Between 10-18 weeks, there is an increase in APRI score, and this increase is the most distinct in the group stratified by EGA, with the lowest EGA having the greatest increase. Beyond 18 weeks, APRI scores continue to rise with little separation among groups in all stratifications. Conclusion: The calculated APRI score clearly delineates fibrosis grade on biopsy in this group. All subgroups demonstrate a clear increase in APRI beginning at 8 weeks with a second increase at 18 weeks. Infants less than 1-year of age who are PN-dependent must be monitored closely for the development of irreversible liver fibrosis.
ELEVATED LEVELS OF CIRCULATING MICROPARTICLES IN DISSEMINATED INTRAVASCULAR COAGULATION AND THEIR IMPACT ON INFLAMMATORY PROCESS
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Disseminated intravascular coagulation (DIC) represents one of the most catastrophic coagulopathies, which results in the simultaneous activation of thrombotic and hemorrhagic processes. The pathophysiology of DIC, and the role of inflammation and Microparticles (MPs) is not fully understood. MPs represent small phospholipid-expressing, procoagulant vesicular fragments, which are released from platelets, leukocytes, and endothelial cells due to cellular disruption and apoptosis. This study was designed to measure functional MPs in 100 random patients from a population of patients diagnosed with DIC. Plasma samples from 30 normal male and female volunteers were used as control. A commercially available functional MP method based on Annexin trapping was used for the determination of the procoagulant activity of MPs (Hyphen Biomedical, Paris, France). The Mean ± Standard Deviation concentration of MPs in the DIC group was 24.6 ± 14.2 nM (Range: 0.0 – 60.0 nM), which was significantly higher than the concentration in the Normal Human Plasma (NHP) control group: 8.5 ± 4.3 nM (Range: 1.3 – 17.4 nM). The distribution curves and the scattergram showed that the MPs concentration in the DIC samples was more widespread than in the NHPs. This study clearly demonstrates that MPs are upregulated in patients with DIC and may mediate the hemostatic activation and inflammatory responses in this syndrome.

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.
VULNERABILITY TO SEPSIS IN THE AGED IS LINKED TO REDUCED PROTEIN C PATHWAY ACTIVATION
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Sepsis, a life-threatening medical condition in which the immune response to infection becomes dysregulated, is a particularly serious problem in the geriatric population as elderly patients with sepsis suffer much higher morbidity and mortality than younger patients. The protein C (PC) pathway is an important anti-coagulant mechanism that prevents disseminated intravascular coagulation, a characteristic late complication of sepsis which often leads to tissue ischemia, multiple organ failure and death. In this pathway, PC becomes activated by a complex of protein interactions including thrombomodulin (TM), an endothelial cell membrane receptor that accelerates the conversion of PC to activated protein C (APC) and results in down-regulation of pro-coagulant factors. The purpose of the present study was to understand why mortality to sepsis increases with advancing age and how coagulation plays a major role in age-associated mortality. Two mouse models of sepsis were utilized in this study: 1) acute endotoxemia by injection with bacterial endotoxin lipopolysaccharide (LPS); and acute peritonitis by cecal ligation and puncture (CLP). Induction of acute endotoxemia in young and aged mice with a low dose of LPS (2.5 mg/kg) caused high mortality in aged (80%) but not young (0%) mice. Fibrin formation, a marker of coagulation, was significantly elevated in several tissues from aged mice only; plasma APS levels were increased in young but failed to increase in aged mice; and TM expression was down-regulated in both young and aged mice but more profoundly depressed in the aged. The age-associated increased thrombosis, suppressed APC level and profoundly decreased TM expression were not observed in young mice receiving a high dose of LPS (20 mg/kg) which resulted in a mortality rate (78%) equivalent to that seen in aged mice (2.5 mg/kg). These findings were all confirmed by CLP, a more clinically relevant model of sepsis. Mutant mice with reduced TM expression and deficient protein C activation showed significantly increased fibrin formation compared to wild-type mice after LPS or CLP, suggesting that TM deficiency, as seen in aged mice during sepsis, contributes to increased thrombosis. Taken together, these results demonstrate that protein C pathway activation is suppressed with aging and is responsible, in part, for increased coagulation and high mortality to sepsis in the elderly.
FLUID RESUSCITATION USING INTRAOSSEOUS VASCULAR ACCESS: FLOW RATES WITH LACTATED RINGER’S AND HETASTARCH

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Background: The achievable flow rates of the intraosseous (IO) route of vascular access for initial fluid resuscitation and volume expansion remain undefined. Infusion rates are necessarily slower due to the high hydraulic resistance of the trabecular bone. In order to maximize volume expansion colloids are used in preference to crystalloids, but the higher viscosity of the colloids in conjunction with the high hydraulic resistance may reduce IO infusion rates. Objective: To measure the IO driving pressures of lactated Ringer’s (LR) solution and 6% hetastarch (HES) at various flow rates thru tibial and sternal sites in swine and to estimate the subsequent volume expansion. Methods: A Jamshidi© IO needle and an EZ-IO-AD© IO needle were placed in the sternum and tibial tuberosity, respectively, of 8 Yorkshire pigs (24-35 kg). IO pressures were recorded for sequentially increasing and decreasing changes in infusion rates for HES and LR at both sites. A linear regression of the pressure-flow rates for each site and solution was used to calculate the flow rates at 100 mmHg (gravity) and 400 mmHg (pressure bag). Relative volume expansion after a 10 min infusion was estimated assuming that one ml of HES expands the intravascular volume by one ml, while one ml of LR expands the intravascular volume by 0.33 ml. Results: Mean LR flow rates (ml•min⁻¹) were 23.9±11.5 (tibia-100mmHg), 110.7±54.3 (tibia-400mmHg), 8.1±3.3 (sternum-100mmHg) and 33.6±17.6 (sternum-400mmHg). Mean HES flow rates (ml•min⁻¹) were lower for both sites and pressures and were recorded at 9.7±4.2 (tibia-100mmHg), 35.9±10.7 (tibia-400mmHg), 5.6±2.8 (sternum-100mmHg) and 25.5±13.9 (sternum-400mmHg). The mean volume expansion (ml) for LR was calculated to be 79.7±38.5 (tibia-100mmHg), 368.9±181.1 (tibia-400mmHg), 26.8±11.2 (sternum-100mmHg) and 112.1±58.6 (sternum-400mmHg). The mean volume expansion (ml) for HES was calculated to be 96.5±42.5 (tibia-100mmHg), 358.9±107.5 (tibia-400mmHg), 56.2±27.6 (sternum-100mmHg) and 255.0±139.4 (sternum-400mmHg). Conclusion: Flow rates for HES were 72% lower than flow rates for LR in the sternum and 36% lower than flow rates for LR in the tibia. Calculated volume expansion with HES represented 218% of the volume expansion of LR when infused via the sternum. There was no significant difference in estimated volume expansion when infusing HES versus LR via the tibia. Rapid resuscitation using the IO route may require a pressure bag or high pressure pump delivery.

HEPATIC DYSFUNCTION AND MELD SCORES IMPROVE AFTER ORTHOTOPIC HEART TRANSPLANTATION AND PREDICT POST-TRANSPLANTATION MORTALITY

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Background: Advanced heart failure (HF) is associated with congestive liver fibrosis and cirrhosis due to increased venous pressure and reduced hepatic blood flow. This results in impaired hepatic protein and lipid synthesis and detoxification of metabolites. No large study has systematically evaluated the incidence of liver dysfunction before and after cardiac transplantation and its impact on survival. Objective: We hypothesized that hepatobiliary markers and the composite MELD score are abnormal in patients with HF, normalize after cardiac transplantation, maintain long-term normalcy and effect clinical outcome and mortality post-transplantation. Methods: Data of 778 adult patients undergoing orthotopic heart transplantation at CUMC/New York Presbyterian Hospital between January 1999 and May 2009 were analyzed retrospectively. Deviation from institutional normal ranges was used to define abnormal liver function (AST, ALT, total bilirubin), biliary dysfunction (serum alkaline phosphatase, GGT), and abnormal hepatic protein synthesis (total protein, albumin, PT, PTT, INR). The MELD Score was calculated using the Kamath formula. Patients with hepatitis, hepatic tumors, biliary diseases, bone diseases, and neoplasias were excluded. Kaplan-Meier survival curves were analyzed by log rank test. Results: The population studied consisted of 76% males with a mean age of 53 +/- 12.1 years, a mean BMI of 26 +/- 4.8 and a mean ejection fraction of 18.6 +/- 9.12. Etiology of HF was 40% ischemic, 38% dilated and 9% idiopathic. Before cardiac transplantation, AST, ALT and total bilirubin were elevated in 18, 10 and 22% of the population, respectively. Total protein and albumin were decreased in 9 and 21% of the population, respectively, and PT, PTT and INR were elevated in 89, 61 and 33% of the population, respectively. By 6 months post-transplantation, all values decreased significantly except ALT and total protein and stayed at this level for 5 years. Patients with a pre-transplantation MELD score of greater than 14 had worse survival after cardiac transplantation (p-value = 0.0036). Conclusion: In this large, single-center retrospective study, we demonstrate a significant improvement in liver dysfunction after cardiac transplantation. Liver dysfunction before transplantation reflected by higher MELD scores has a significant impact on long-term survival of patients after cardiac transplantation.
THE ROLE OF LAPAROSCOPIC EVALUATION TO DETECT A CONTRALATERAL DEFECT AT INITIAL PRESENTATION FOR INGUINAL HERNIA REPAIR

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Background: Management of the contralateral side in children presenting with unilateral inguinal hernias is controversial. Particularly, the accuracy of laparoscopic (lap) evaluation for a contralateral patent processus vaginalis (CPPV) by passing a scope through the hernia sac has long been a subject of debate. Objective: This objective of this review was to determine the accuracy of lap evaluation to detect a contralateral defect at initial presentation for inguinal hernia (IH) repair and the rate of CPPV relative to age, sex, and initial side. Methods: This is a retrospective review of 1508 infants and children with unilateral IH treated at a single institution between 5/1/04 and 11/24/09. Eight pediatric surgeons performed the procedures and selectively utilized laparoscopy for detection of CPPV. Cases were evaluated for age, post-conceptual age, sex, side of initial hernia presentation, incarceration, presence of comorbid conditions, and procedure performed. Comparisons were performed using chi-square tests. Results: There were 1205 (80%) boys and 303 (20%) girls; 980 (65%) presented with right IH (RIH) and 528 (35%) with left IH (LIH). 330 (22%) were premature. The median age was 1.1 years, with 43% <6 months. Associated conditions were incarceration (9%), abdominal wall defects (1%), and ventriculoperitoneal shunt (1%). Lap evaluation was done in 459 (47%) patients presenting with RIH, and 225 (43%) patients presenting with LIH. Lap evaluation was positive for CPPV in 32% of RIH, and 42% of LIH (p=0.0168). CPPV detection by age was: premature (46%); <6 months (45%); 6 to 12 months (24%); 1 to 2 years (19%); and >2 years (24%). CPPV was also associated with prematurity (p=0.0003) and age <6 months (p=0.0001), but not with sex (p=0.55). In patients without lap evaluation, the contralateral occurrence was 4.4% (mostly from left-sided occurrence after RIH). Those with negative lap evaluation for CPPV had future contralateral occurrence of 1.6%. Conclusions: The highest rate of CPPV is in premature infants, infants <6 months of age, and children presenting with LIH. Although the rate of CPPV is lower after 6 months of age, girls >2 years of age have a significantly higher rate of CPPV than boys, supporting lap evaluation in older girls. Those selected for only unilateral repair had a low rate of subsequent contralateral hernia; children with a negative lap evaluation had a low but not negligible rate of developing future contralateral hernia.

ELECTRONIC MONITORING IMPROVES BRACE WEARING COMPLIANCE IN PATIENTS WITH ADOLESCENT IDIOPATHIC SCOLIOSIS

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Background - Spinal bracing is the non-operative standard of care among skeletally immature patients with a diagnosis of adolescent idiopathic scoliosis (AIS) once the spinal curvature has reached 20-25°. Several studies have suggested that the use of a spinal brace positively affects the natural history of curve progression in some patients. Efficacy of brace wearing has been shown to be "dose dependent," with improved outcomes observed when the brace is used full time. A recognized barrier to effective brace treatment is patient noncompliance. Although many studies have been conducted on the effect of medication monitoring on patient compliance, few studies have attempted to measure the effect of compliance monitoring on orthotics use. Objective - To determine if electronic monitoring effects brace wearing compliance in patients with AIS. Study Design - Randomized controlled trial. Methods - 21 skeletally immature patients (mean age=12.4) with previously untreated AIS were prescribed treatment with a custom made Thoraco-Lumbo-Sacral-Orthosis (TLSO) for 18 hours/day. A StowAway TidiT temperature probe was hidden from view within each TLSO to measure brace compliance. 10 patients were randomized to be informed that their compliance was monitored whereas 11 patients were unaware that monitoring was taking place. Data from the temperature probe was uploaded to a personal computer at the 4 month follow up visit and used to generate a profile of brace wearing throughout the observation period. Results - Mean daily brace wear for patients informed about monitoring was significantly higher than patients uninformed that their compliance was being monitored (15.4 hours per day vs. 10.2 hours per day, p=0.03) over 14 weeks of observation. Conclusions - Patient knowledge of monitoring of brace wearing compliance has been shown to significantly increased adherence with spinal orthoses over a 14 week period. This present study suggests that compliance monitors may improve adherence with brace protocols in patients with spinal deformity or other orthopaedic pathologies necessitating long term orthotic intervention.
INTRODUCTION: One of the most important determinants for successful endovascular repair of abdominal aortic aneurysms (EVAR) is adequate infrarenal aortic neck length. While a minimum neck length of at least 15 mm is optimal, patients with shorter neck lengths may be considered if medical comorbidities prohibit open repair. We reviewed our experience with EVAR in patients with short (<15mm) infrarenal necks focusing on the incidence, treatment and midterm outcome of proximal attachment site endoleaks.

METHODS: We reviewed 371 AAA patients who underwent EVAR between December 2000 and July 2008. Ninety-three patients (25%) were identified who had an infrarenal aortic neck length less than 15 mm. All Ancure grafts (n=38) were excluded leaving 55 patients with short (≤15mm) infrarenal necks. The mean neck length was 9.3±2.7 mm (range 4-14mm) with a mean preoperative aneurysm size of 6.2±12cm.

Endovascular grafts implanted were 11% Excluder (n=6), 24% AneuRx (n=13), and 65% Zenith (n=36). Mean follow-up was 16±15 months (range 1-71 months). RESULTS: Seven (1 AneuRx, 1 Excluder, and 5 Zenith) proximal endoleaks were recognized on first completion angiogram in the operating room (OR). Five of these were sealed intraoperatively with additional balloon angioplasty and/or proximal extension cuffs. One patient had a persistent small type one endoleak intraoperatively despite an extension cuff and Palmaz stent. The leak resolved after 1 month. Two additional patients developed late type I endoleaks (2 AneuRx). Both were successfully treated with a proximal extension cuffs. The overall incidence of postoperative type I endoleaks was 2/55 (4%). There were no ruptures or aneurysm related deaths. Mean aneurysm size decreased to 5.3±1.4 cm at a mean of 16±15 months. CONCLUSIONS: Our data suggests that acceptable midterm results can be achieved when performing EVAR in patients with short (<15mm) infrarenal necks. Therefore, AAA patients with severe comorbidities and short infrarenal neck lengths (4-14mm) should not be denied EVAR based on short neck length alone. Longer term data will be needed to determine durability of EVAR in these patients.

COMPLICATIONS OF LOW-PROFILE DORSAL VERSUS VOLAR LOCKING PLATES IN THE DISTAL RADIUS: A COMPARATIVE STUDY

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Hypothesis: Volar locking plates have gained widespread acceptance due to a high incidence of extensor tendon complications associated with traditional 2.5mm dorsal plates. A new generation of 1.2-1.5mm 'low-profile' dorsal plates was designed to minimize tendon irritations. This study compares the complication rates of low-profile dorsal plates to volar locking plates. Methods: 117 patients with distal radius fractures were eligible for this study. Patients were excluded if they had fractures requiring external fixation, had no postoperative follow-up, were deceased at the time of phone follow-up, or had "sandwich" plating. Those with less than 12 months follow-up were contacted by phone, and those who could not be reached were considered lost to follow-up (17 patients, 15%). Information pertaining to seven categories of complications (hardware discomfort/pain, tendon irritation, failure of reduction, infection, complex regional pain syndrome, stiffness, neuropathy/hypersensitivity) was collected through medical record review and phone interviews. Post-operative plating complications requiring surgical intervention were considered major complications and those that did not were considered minor complications. Results: 100 patients, comprising 104 plating cases (57 dorsal, 47 volar), were included in this study. Length of follow-up was 49±21 (13-80) months for dorsal plates and 38±19 (12-72) months for volar plates (p=0.003). Fifty-six cases (28 dorsal, 28 volar, p=0.33) had some form of complication. One dorsal and 3 volar plates resulted in radiographic failure of reduction (p=0.33). Three dorsal and 4 volar cases had complete plate removals (p=1.0). Four dorsal and zero volar plates had screw removals only (p=0.12). Three dorsal and 3 volar plates had major tendon irritation complications, and 4 dorsal and 3 volar plates (p=0.37) had minor tendon irritation complications. Four volar cases and zero dorsal cases had major neuropathy complications (p=0.04). Gender and age did not result in significantly different complication rates. Conclusions: The difference in complication rates between low-profile dorsal plates and volar locking plates is minimal. However, volar plating/surgery is associated with a higher rate of neuropathic complications.
Poster 1
VENTRICULAR ASSIST DEVICE IMPLANTATION REVERSES IMPAIRED MYOCARDIAL METABOLISM AND LIPOTOXICITY IN ADVANCED HEART FAILURE
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Background: In advanced heart failure (HF), myocardial substrate metabolism shifts from primary utilization of fatty acids to oxidation of glucose for generation of ATP. This is associated with defects in mitochondrial biogenesis, suppression of fatty acid oxidation genes and decreased oxidative metabolism. This potentially leads to accumulation of toxic lipid intermediates and cardiac dysfunction. Implantation of ventricular assist devices (VAD) mechanically unloads the failing heart and may also correct metabolic abnormalities in patients with advanced HF.Objective: We hypothesized that metabolic derangements in patients with HF will reverse after hemodynamic improvement through VAD placement. Methods: We analyzed clinical data and myocardial tissue samples from patients with advanced HF undergoing VAD implantation and explantation at CUMC/New York Presbyterian Hospital. Total mRNA was extracted and mrNA levels of metabolic genes were analyzed by RT-PCR. Myocardial triglycerides were extracted using the Folch method. Clinical data were obtained for all patients from institutional electronic medical records. Results: We analyzed a cohort that consisted of 80% males with a mean BMI of 27.1 +/- 5.1 kg/m2, mean age at LVAD implantation of 51 +/- 12.1 years and mean duration of LVAD for 195 +/- 158.9 days. Records showed a history of T2DM in 32%, hypertension in 51% and smoking in 46% of cases. The etiology of HF was ischemic in 46% and dilated in 54% of cases. Relative expression of myocardial lipid metabolism genes CD36, CPT1, and ACO increased 1.6 +/- 1.66, 4.3 +/- 7.57, and 1.2 +/- 1.36 fold, respectively, after VAD implantation. Relative expression of glucose oxidation genes decreased with GLUT4 at 0.7 +/- 0.21 fold and PDK4 at 0.45 +/- 0.31 fold. Levels of cardiac triglycerides decreased from 2.75 to 1.05 ug/mg tissue after VAD implantation. An overall improvement in hematologic indices, renal and hepatic function was noted after VAD implantation. Fasting glucose decreased from 135.9 +/- 38.11 to 106.5 +/- 28.54 mg/dL (p-value < 0.001) indicating an improvement in overall metabolism with a correction of insulin resistance. Conclusion: Hemodynamic improvement after VAD implantation increased fatty acid oxidation, increased triglyceride lipolysis and decreased glucose oxidation with an improvement in systemic insulin resistance. These data indicate that lipotoxicity in advanced HF reverses after mechanical unloading of the failing heart.

Poster 2
OBSTRUCTIVE SLEEP APNEA: EFFECTS OF CONTINUOUS POSITIVE AIRWAY PRESSURE ON CARDIAC REMODELING AS ASSESSED BY CARDIAC BIOMARKERS, ECHOCARDIOGRAPHY AND CARDIAC MRI
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BACKGROUND: Obstructive sleep apnea (OSA) is associated with an increased risk of cardiovascular morbidity and mortality. Although previous echocardiographic studies have demonstrated short-term improvement in cardiac remodeling in OSA patients on continuous positive airway pressure (CPAP), a long term study incorporating cardiac biomarkers, echocardiography and cardiac magnetic resonance imaging (CMR) has not been performed to date. OBJECTIVE: To determine the long term benefits of CPAP on both right and left ventricular systolic and diastolic function in patients with OSA using serial cardiac biomarkers, echocardiography and CMR. METHODS: A prospective study of 50 OSA diagnosed patients was performed between 2007 and 2009 inclusive. Cardiac biomarkers including C-reactive protein (CRP), N-terminal pro-B-type natriuretic peptide (nt-proBNP) and troponin T (TnT) were measured at baseline and serially over one year. All patients underwent baseline and serial transthoracic echocardiography (TTE) and CMR to assess for cardiac remodeling. RESULTS: Following 12 months of CPAP therapy, levels of CRP, nt-proBNP, and TnT did not change significantly from normal baseline values. As early as 3 months, TTE revealed an improvement in left ventricular end-diastolic diameter (59±5mm to 52±4mm), right ventricular end-diastolic diameter (41±3mm to 36±5mm), and the degree of pulmonary hypertension (54±6 mmHg to 42±4 mmHg), which continued to improve over one year of follow-up. Left atrial filling pressures decreased from 16±3 to 8±2 at 12 months. Finally, LV mass, as determined by CMR, decreased from 185±4 g/m2 to 162±3 g/m2 as early as 6 months into CPAP therapy and continued to improve until completion of the study at one year. CONCLUSIONS: Both systolic and diastolic abnormalities in OSA patients can be reversed as early as 3 months into CPAP therapy, with progressive improvement in cardiovascular remodeling over one year, as assessed by TTE and CMR.
INCREASED 90-DAY MORTALITY IN ACUTE HEART FAILURE PATIENTS WITH ELEVATED COPEPTIN LEVELS
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Background: In heart failure (HF) patients, increased arginine vasopressin (AVP) activity is associated with poorer prognosis, making AVP an attractive target for therapy. However, AVP is difficult to measure due to its instability and rapid clearance. Copeptin, the C-terminal segment of pre-pro-vasopressin, is a stable and sensitive biomarker for AVP release. Objective: This analysis sought to investigate the prognostic utility of copeptin in patients presenting to the emergency department (ED) with acute dyspnea. Methods: The BACH trial was a prospective, 15-center diagnostic and prognostic study of 1641 patients with acute dyspnea. A secondary endpoint of the study was to evaluate the prognostic utility of copeptin in patients diagnosed with acute HF. Patients were followed up for 90 days after initial evaluation. Results: 556 patients had a final diagnosis of HF. Patient with copeptin levels in the highest quartile had increased 90 day mortality (p<.001). Patients with copeptin levels above median (1.43 pmol/L) and sodium levels below median (139 mEq/L) also had increased 90 day mortality (p=.004). In high and low sodium groups based on median split, mortality is increased in the highest copeptin quartile in both groups. Of note, there is poor correlation between copeptin and sodium (R=0.47). Conclusion: This large scale study has shown significantly increased 90-day mortality in patients with elevated copeptin, especially in those with copeptin levels in the highest quartile. These findings provide a crucial piece of prognostic information in patients with acute HF, making it feasible for future guided AVP antagonist therapy in HF patients with elevated copeptin levels.

IDENTIFICATION OF CARDIOMETABOLIC RISK IN MEDICAL STUDENTS.
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OBJECTIVE: To determine the prevalence of cardiometabolic (CMR) risk factors in medical students of a government medical college of Karachi. SUBJECT AND METHODS: We conducted a cross-sectional study on students of Dow Medical College, Karachi, Pakistan. Measurements were taken for assessing blood pressure, height and weight. A pretested self-administered questionnaire was used to collect other data. Blood pressure and height/weight (for calculating BMI) was noted by trained observers and physical activity level was determined through the WHO Global Physical Activity Questionnaire (GPAQ). SPSS 15.0 was used for statistical analysis. Cardiometabolic risk was determined on the basis of presence of elevated blood pressure, personal or family history of cardiovascular disease (CVD), overweight, smoking, alcohol consumption, low physical activity level, incorrect self-assessment (underestimation) of weight, low knowledge about cardiometabolic risk factors and lack of interest in consuming cardioprotective diet. An arbitrary scale was made for assessing cardiometabolic risk on the basis of above mentioned risk factors. Score obtained by each student on CMR scale was calculated. RESULTS: Non-probability purposive sampling was used and a total of 132 medical students were included in the study of which 57 (43.2%) and 75 (56.8%) were male and female respectively with overall mean age of 20.85 ± 1.21 years. Males had significantly higher mean cardiometabolic risk score as compared to females. This was largely due to difference in presence of elevated blood pressure (43.9% males vs. 14.7% females, p = 0.000), lack of interest in consuming cardioprotective diet (26.3%ma vs. 2.7%f, p = 0.000) and underestimation of weight (14%m vs. 0%f, p = 0.01). Family history of CVD (57%) and low physical activity level (38%) were the most common cardiometabolic risk factors. CONCLUSION: Presence of family history in large number of students, high rates of elevated blood pressure and lack of knowledge and interest in modifying behavior indicate urgent need for motivating students for taking interest in their own cardiometabolic health. The situation reflects potential of future physicians for encouraging their patients to modify their health related behavior.
Background: Smoking is a primary risk factor for coronary vascular disease, however, few studies focus on the pathogenesis of cigarette smoke and cardiac remodeling. Objective: Using a rodent model of cardiac disease, via the aortocaval fistula model of chronic volume overload, we evaluated the hypothesis that ventricular remodeling and dysfunction is worsened by cigarette smoke. Methods: Four groups of Sprague-Dawley male rats were studied: sham-operated controls (SHAM), SHAM exposed to cigarette smoke (SHAM+SMK), volume-overloaded (FIST), and FIST exposed to cigarette smoke (FIST+SMK). Smoke exposure consisted of six Kentucky 2R4F cigarettes per day for the duration of six weeks. Cardiac structural and functional changes were assessed weekly by ultrasound echocardiography for the 6 week study period. Ventricular collagen volume fraction (CVF) was calculated from picrosirius red stained left ventricular (LV) sections. Results: Analysis of Cardiac Function: temporal echocardiogram demonstrated a significant increase in the diameter of the LV and a marked decrease in fractional shortening (p<0.05 vs. untreated FIST). Analysis of collagen matrix: CVF data revealed that not only did the SHAM+SMK rats experience a 15% reduction of collagen compared to SHAM rats, but the FIST+SMK rats developed a significant 45% loss of collagen compared to FIST rats (P<0.05). Conclusions: These data demonstrate that cigarette smoke exacerbates the loss of ventricular collagen in response to volume overload, which likely contributes to ventricular dilation and dysfunction. Further studies warrant an investigation to evaluate the mechanisms that contribute to collagen remodeling of the extracellular matrix.

Poster 6
FORTILIN AUGMENTS ATHEROSCLEROSIS FORMATION IN A HYPERLIPIDEMIC TRANSGENIC MOUSE MODEL
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Fortilin, first characterized in 2001, is a structurally unique intracellular protein that is not only ubiquitous in a wide range of human tissue, but also highly conserved across species. Subsequent studies have found that fortin has an essential role in cellular proliferation by inhibiting effector caspases and thereby negatively regulating the apoptotic pathway. To determine whether fortin affects atherosclerosis, a pro-inflammatory disease associated with lipid-laden macrophage differentiation and proliferation, a transgenic mouse model was developed. Five male fortin homozygous (fortin +/+), LDL receptor-deficient (LDL -/-), apobec1 deficient (apobec1 -/-) mice and twelve male fortin heterozygous (fortin +/-), LDL -/-, apobec1 -/-, mice* were generated to compare the effects of fortin on atherosclerotic progression in a hyperlipidemic state. After 44 weeks on a standard chow diet, the extent of atherosclerotic plaque formation was quantified in the mice aorta (measured as a percent of total surface area). In addition, aortic valve tissue was stained for markers of cellular proliferation and apoptosis. There was a significant increase in atherogenesis in the fortin +/- group compared to the fortin +/- group (43.2±5.5% vs. 33.3±7.7%, p<0.05). These results demonstrate that the presence of the anti-apoptotic protein fortin has a role in facilitating atherosclerotic plaque formation and may be an important molecular target for the future therapeutic treatment of vascular disease.
Poster 7
TRACKING ACNE LESIONS LEADING TO SCAR FORMATION WITH COMPUTER-ASSISTED ALIGNED PHOTOGRAPHS.
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Once formed, postacne scars are resistant to treatment and can have serious psychosocial consequences, including social isolation and exacerbation of psychiatric disease. These scars are attributed to deep dermal tissue injury secondary to inflammation; damage limited to the epidermis or papillary dermis is usually only transient. Due to the superficial, noninflammatory nature of comedones, these lesions are presumed rarely contributory to scarring, but their actual contribution is unknown. The objective of this study was to evaluate the progression of inflammatory and non-inflammatory acne lesions into scars. Digital images collected from 2 previous studies were used. Standardized lateral facial photographs were taken of subjects with untreated facial acne at baseline and every 2 weeks for 12 weeks. The evolution of individual acne lesions was tracked over time, using 6 predefined acne lesion categories: open/closed comedones, erythematous macules, papules, pustules, and nodules. To facilitate tracking, the images were computer aligned to reduce inconsistencies with positioning between serial photographs. A region of interest (ROI) with the most clinically significant acne was selected and magnified by 211%. With the magnified serial ROI images of 22 individuals, evaluators identified atrophic acne scars using categories adapted from the Jacob et al criteria: ice pick (0.5-<1.5mm), boxcar (1.5-4mm), and rolling (>4mm). Scars were then tracked to the corresponding lesions at baseline. 20% of the scars correlated to acne lesions. Of the identified ice pick scars in week 12, 6.9% were associated with inflammatory papules, 4.1% with closed comedones, and 2.8% with erythematous macules at baseline. Of the identified boxcar scars, 13% correlated to pustules, 3.3% with inflammatory papules, 3.3% with closed comedones, and 1% with erythematous macules at baseline. Of the 2 rolling scars identified in week 12, 1 was associated with an inflammatory papule and 1 with an erythematous macule at baseline. Our results support the contribution of inflammatory acne in postacne scarring, particularly in the development of more severe scars. However, this study also evidences the role of macular and comedonal disease in scarring. We thereby suggest that all forms of acne should be treated, and greater measures should be taken to manage mild acne. Further studies are necessary to understand the role of non-inflammatory acne in atrophic scar formation.

Poster 8
RELEVANCE OF PROTEIN MISFOLDING IN CUTANEOUS DISEASES
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Background: Certain dermatological illnesses are the results of alterations in a protein’s structure, leading to the malfunction or aggregation of the protein. There are many diseases that share this pathogenesis; Macular, Lichen, Nodular Cutaneous Amyloidosis. Cutaneous Amyloidosis has been related to many types of skin cancer. In protein misfolding diseases, the exact mechanism that converts a protein’s structure is unknown, but emerging insights believe a common toxic protein intermediate could be responsible for the tissue damage and dysfunction that results from these diseases. Objectives: Immunohistocharacterization of different samples of Lichen and Macular Cutaneous Amyloidosis, Basal and Squamous Cell Carcinoma, utilizing conformational antibodies, is a reliable method to gain insight into the different stages and forms of amyloidogenic proteins. Conformational antibodies have the ability to recognize and bind different amyloid species such as fibrils and oligomers; this will be helpful in allowing us to visualize what amyloid species the misfolded proteins are assuming, and their origin. Methods: The immunohistocharacterization will be done on human fixed paraffin sections, which received a clinical and histopathological diagnosis of amyloidosis. The sections will be prepared with our novel antibodies and with traditional amyloid staining techniques. The sections will be analyzed with light, polarized, and confocal microscopic methods to assess the presence of amyloid, distribution and staining pattern, conformation of the protein, and location in relation to keratinocytes and other cells present in the skin. Different biochemical assays will also be performed on fresh tissue homogenates for detection of protein aggregates. Results: In our preliminary studies we were able to characterize lichen and macular cutaneous amyloidosis with conformational antibodies, and detect mis-folded proteins in skin cancer. Several forms of amyloid species were identified and detected in all deposition diseases, most importantly amyloid oligomers the species thought to be the most toxic among protein aggregates. Conclusions: The use of these antibodies could be used for a generic detection and removal of protein aggregates which may lead to treatment of these diseases.
Background: Ultraviolet light (UVL) exposure is a known risk factor for developing skin cancer. However, while UVL is a major risk factor for scalp cancer, the types of protective measures taken to avoid UVL scalp damage remains less studied. Objective: Evaluation of the impact of hair loss and other factors on UVL protective behaviors and the development of cutaneous cancer of the scalp. Methods: A cross-sectional survey was designed to compare the awareness and protective behaviors of beachgoers in regards to skin and scalp cancer in an environment with high natural UVL exposure. Data were collected about subjects’ age, gender, Fitzpatrick skin type (FST), hair loss, UVL skin and scalp protection behaviors, and baseline knowledge about the causes of skin and scalp cancer. Results: A total of 248 questionnaires were completed and analyzed. These questionnaires included data from 153 (62%) participants with no reported hair loss and 95 (38%) participants with self-reported hair loss. When scalp protection was compared with skin protection there was a significant difference (p<.001) in rates of UVL skin protection (50%) and UVL scalp protection (16%). There also exists significant association (p<0.0001) between hair loss and sun protection factor (SPF) use on the scalp. That is, subjects with mild hair loss (2A to 3V on questionnaire) are more likely and subjects with advanced hair loss (4 or greater on questionnaire) are even more likely to use sunscreen on their scalp than those who do not have hair loss (21% and 38%, respectively, vs. 7%). Significant association (p=0.0008) also exists between hair loss and hat use, as well as significant association (p=0.0035) between visibility of scalp and hat use. Sixty-eight percent of 248 survey respondents scored high (two correct answers) for awareness of UVL damage to skin. However, only 48% of 248 respondents scored high for awareness of the influence of UVL on hair loss/scalp damage. A high degree of awareness of UVL damage to skin is more likely than a high degree awareness of the influence of UVL on hair loss and scalp damage (p<0.0001). Conclusion: This study demonstrates a low rate of SPF scalp (16%) protection. In addition, this study shows that subjects become increasingly likely to use sunscreen or a hat on their scalp as they lose more hair. However, even with advanced hair loss, only 38% of subjects used SPF on their scalp. More public education focused on UVL scalp protection is needed.

Poster 10
PHOTOACTIVATED ROSE BENGAL, A MUTAGEN?
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Dermatological surgery relies on sutures and adhesives for wound closures. These methods increase the risk of foreign body reactions, infection, and scarring, not to mention the psychological impact this may have on patients. Recent studies have investigated Rose Bengal (RB) as a photochemical bonding agent to replace traditional wound closure techniques. Once photoactivated, RB is known to create reactive oxygen species (ROS), such as singlet oxygen, which can lead to DNA mutations. In this study, we investigated the toxicity and mutagenicity of photoactivated RB on epithelial Chinese hamster ovary (Cho) cells. Cells were exposed to the following concentrations of RB: 0.1%, 0.01%, 0.001%, and 0.0001%. The cultures were irradiated for 400 seconds using a high-intensity visible wavelength lamp at 81,500 lux, and controls were maintained in the dark. Cell viability was assessed using trypan blue exclusion and the XTT assay, and mutagenicity was assessed using the Hprr gene mutation assay. Exposure to concentrations of RB greater than 0.001% resulted in complete cytotoxicity following exposure to light. After 30 minutes and 24 hours, the XTT assay showed that cells exposed to light only, the lower levels of RB without light, or the lowest level of RB plus light appeared more viable than controls without light. The Hprr gene mutation assay showed that the light activated RB at 0.0001% was likely mutagenic, roughly doubling the mutant frequency above background. All other concentrations resulted in low or nonexistent colony formation due to RB's cytotoxicity. RB's ability to produce ROS and its potential for mutagenicity should be taken into consideration in its clinical application. RB's innate cytotoxicity at relatively low concentrations (e.g., 0.001%) appears to be significantly below the 0.1% concentration used in clinical studies. The contribution of this cytotoxicity on the observed clinical improvement of scars is unclear and warrants further investigation.
Poster 11
PRESENTATION OF SKIN CANCERS IN LATIN AMERICANS AS RELATED TO THEIR ACCESS TO HEALTHCARE
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Background: Skin cancer is a major problem for many Americans. The incidence of skin cancer is currently on the rise. Between 2 and 3 million non-melanoma skin cancers and 132,000 melanoma skin cancers occur globally each year. The mortality rate from melanoma is much higher compared to basal cell carcinoma and squamous cell carcinoma. Therefore, not much attention has been paid to basal cell carcinoma and squamous cell carcinoma in terms of access to care for a timely diagnosis. Although the risk of distant metastasis from basal cell carcinoma is extremely low and metastasis from melanoma compared to squamous cell carcinoma is much more likely, the risk is not zero and these cancers tends to cause local invasion of surrounding structures where Latinos may be at an increased risk. There are many factors that play a role in delayed diagnosis of skin neoplasms in Latinos including lack of awareness of skin cancer, distance from a medical institution, lack of insurance, and a limited number of dermatologists as well as intrinsic factors including Fitzpatrick skin type and cultural differences. However, it is to be determined which factor(s) limit this the most and whether any of these factors are ethnic-dependent. Objective: The researcher hypothesizes that the further away the patient lives from the primary medical institution leads to a delayed diagnosis of basal cell carcinoma and squamous cell carcinoma determined by tumor size in the Latino population compared to non-Latinos when diagnosed by a dermatologist. Methods: A retrospective chart review from archives and the electronic medical record was undertaken under proper guidance of the IRB. Dermatopathology reports were compared with patient charts and evaluated for reported ethnicity, tumor size, location and number. Patient medical history was examined for reasons of exclusions. Patient addresses at the time of diagnosis were also recorded and distance from UTMB was calculated. Analysis of variance for each measure of thickness of tumor was assessed to determine the impact of ethnicity and distance. Results and Conclusions: Preliminary data show that Latinos have larger tumors at diagnosis, but this does not necessarily correlate with distance.

Poster 12
EFFECTS OF SHORT AND LONG-TERM TITANIUM DIOXIDE NANOPARTICLE EXPOSURE ON CHINESE HAMSTER OVARY CELL VIABILITY
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Titanium dioxide (TiO2) is used in sunscreens and cosmetics for its effective blocking of Ultraviolet (UV) light penetration into the skin, which helps decrease the risk for UV damage and skin cancer. Recently, nano-sized TiO2 has been incorporated into sunscreens, because it leaves less opaque residue on the skin, making these products more cosmetically appealing. However, limited evidence has shown that nanoparticles have the potential to enter the body more easily due to their small size. We first performed a short-term exposure using a range of TiO2 concentrations to assess cell viability using the Chinese hamster ovary (Cho) cell line. Using trypan blue exclusion, we found that cell viability was not significantly affected. We were able to visualize nanoparticles located within cell phagosomes using electron microscopy. To more accurately mimic the chronic use of these products on humans, we carried out a long-term exposure study with a range of TiO2 concentrations. Cells were maintained under exponential growth conditions for 60 days and were continuously exposed to either 10, 20, or 40 μg/ml TiO2 (<25 nm) nanoparticles suspended in dimethylsulfoxide. We assessed the effects on reactive oxygen species (ROS) production, DNA content, and cell cycle. Even after long-term exposure, no significant effects on viability or proliferation were apparent using the XTT assay. ROS levels increased in a time- and concentration-dependent manner using the ROS reactive dye, dihydrorhodamine 123. Variation in DNA content and the number of cells in the G2+M phase of the cell cycle increased in a concentration-dependent manner suggesting negative effects on DNA replication and cytokinesis. Neither short- nor long-term exposure to TiO2 nanoparticles seemed to affect viability. Our data suggest that chronic, continuous exposure to low levels of nano-TiO2 increases oxidative stress, and impacts the cell cycle and genetic material in a sub-toxic and sub-lethal manner. With chronic exposure to these particles, these changes that have not been lethal in vitro, may cause adverse effects in humans.
FORMATION OF BLOC-2 AND BLOC-3 AND THEIR ROLES IN THE TRAFFICKING OF TYROSINASE PROTEINS
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Background: Biogenesis of lysosome-related organelles complexes (BLOCs) have been shown to mediate the trafficking of melanocyte-specific gene products from their site of synthesis in the trans-Golgi network to their site of action in the melanosome, the organelle responsible for skin pigmentation. Mutations in the BLOCs result in a form of oculocutaneous albinism called Hermansky-Pudlak syndrome (HPS), which is also characterized by a bleeding diathesis and pulmonary fibrosis. BLOC-2 is known to contain at least HPS 3, HPS 5 and HPS 6. BLOC-3 is known to contain at least HPS 1 and HPS 4. Objectives: Initially, this study aimed to confirm the known members of the BLOC-2 and BLOC-3 complexes. Secondly, known members of BLOC-2 and BLOC-3 were localized in the melanocyte, and colocalized with melanocyte-specific proteins. Lastly, additional novel candidate proteins for the BLOC-2 and BLOC-3 complexes were assessed.

Methods: The molecular weights for HPS 1, 3, 5, and 6 were identified by western blot analysis. Indirect immunofluorescence allowed for the localization of BLOC-2 and BLOC-3 within melanocytes, and the colocalization of BLOC-2 and BLOC-3 with melanocyte-specific proteins, specifically tyrosinase and tyrosinase-related protein 1 (Tyrp1). Immunoprecipitation studies were conducted to determine candidate binding partners to BLOC-2 and BLOC-3.

Results: The molecular weights for the known components of BLOC-2 and BLOC-3 were identified and matched the predicted molecular weights. HPS 6 had an unexpected second band of 140kDa, which was present in light melanocyte lines and absent in dark melanocyte lines. Colocalization of BLOC-2 and BLOC-3 with melanocyte-specific proteins appeared at or near the Golgi network, respectively. Finally, candidate binding partners for BLOC-2 were identified, consisting of a myosin regulatory light chain and cytoskeleton-associated protein. A candidate binding partner for BLOC-3 was also found, heat shock protein 60 (hsp60).

Conclusions: From this preliminary data, we propose that BLOC-2 and BLOC-3 function at upstream and downstream sites, respectively, in melanogenesis. These findings provide additional possible mechanisms for BLOC-2 and BLOC-3 in melanogenesis.

BURNOUT IN PREMEDICAL UNDERGRADUATES
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Burnout is a psychological syndrome which results from a prolonged response to occupational stressors. It consists of three dimensions: emotional exhaustion, cynicism, and a lack of personal efficacy, with high levels of emotional exhaustion or cynicism being indicative of clinically significant burnout. There has been a growing recognition that physicians, residents, interns, and medical students are prone to burnout with recent studies demonstrating an association between chronic burnout and higher rates of suicidal ideation.

Can the symptoms of burnout be identified earlier, in the premedical years? To rectify these gaps in our knowledge, this study aims to survey college students at UC San Diego in order to assess their burnout severity. Our primary hypothesis is that premedical students will exhibit greater burnout severity than non premedical students. As a secondary aim, we will explore the interactions of premedical student status with gender and ethnicity in the context of burnout. We invited all undergraduate biology majors at UC San Diego to participate in a web-based survey. Subjects were also recruited through Experimetrix, a UC San Diego psychology research recruitment program. The survey consisted of demographic questions such as gender, ethnicity, age, graduation date, and premedical status. Also, we used the Maslach Burnout Inventory Student Survey (MBI-SS) to gauge the three dimensions of burnout: emotional exhaustion, cynicism, and a lack of personal efficacy. 667 premedical students and 1540 non premedical students completed the questionnaire. Premedical students showed greater burnout in the dimension of emotional exhaustion than non premedical students. Premedical students had greater personal efficacy than non premedical students. Premedical females had the greatest overall burnout, emotional exhaustion and cynicism when compared with non premedical females and males. Hispanic premedical students had greater overall burnout and greater cynicism than Hispanic non premedical students. These findings emphasize the importance of recognizing the unique strains and mental health consequences of a premedical curriculum, especially for women and certain minority ethnic populations. Longitudinal, multi-institutional research must be done in order to determine etiology with the ultimate intention of identifying opportunities for prevention and early intervention which may provide significant public health payoffs in the long run.
Poster 15
THE PHYSIOLOGICAL “PERFORMANCE WINDOW” FOR INTERNATIONAL SOCCER MATCHES AT HIGH ALTITUDE
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In 2007, citing concerns over players' health and unfair competition, FIFA (world soccer governing body) considered limiting international matches at altitudes exceeding 2000 mts. To the millions of soccer fans in the high altitude countries of South America and Mexico, the news was devastating. Are FIFA's concerns legitimate? Existing medical studies do not support FIFA's position as none of them are based on soccer-specific factors. The legitimacy of FIFA's position must be tested to ensure the well-being of players and prevent the social problems which would accompany the exclusion of some countries from international play. Existing medical research on athletes in high altitudes focuses on mountaineering; there is no research on soccer players playing at high altitudes. My objective was to design and implement tests specifically for competitive soccer, which involves a combination of aerobic and anaerobic states: players run 10-14 km during a match; spurts of intense motion/sprinting are limited, and recuperation opportunities are prevalent. My hypothesis was that there is a “physiological performance window” where a soccer athlete can arrive at high altitude and can perform at a near normal level for 6 hrs after arrival, after which the adaptation process begins. I selected players who live in the city of La Paz, Bolivia (3600 mts) and others who live in Trinidad, Bolivia (100 mts). I designed tests relevant to a high-level soccer match, and applied these in their normal habitat/playing environment. Once these were completed, the athletes were transported to La Paz or Trinidad, and the same tests were applied at 2 hrs, 4 hrs, 8 hrs, 18 hrs and 24 hrs after arrival. The results of the physical performance tests conducted at high and low altitudes did not vary significantly among the players at the 2 hr and 4 hr windows. At the higher altitude, all the players experienced symptoms of acute mountain sickness (AMS) such as headache; however, their maximum aerobic power (VO2max) was only slightly reduced and their ventilation, heart rate and blood lactate were minimally affected. Notably, there were no significant differences in these functions when measured in response to the maximum exercise. The “physiological performance window” is valid, research remains to be done on optimal adaptation including the usage of intermediate altitudes and emerging technologies such as hyperbaric chambers. Finally, the universality of soccer is guaranteed.

Poster 16
INFORMED DECISION MAKING AND ATTITUDES IN PRENATAL GENETIC TESTING – THE FUTURE OF RESEARCH
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Background: Maternal mortality is still at discouragingly high levels, with half a million women dying yearly with some complication related to pregnancy and birth. Prenatal genetic testing (PGT) is a life-saving, preventative intervention that can reduce both infant and maternal morbidity and mortality. However, provided the novelty of this intervention, no universal guidelines have been created for providers to guide informed decision making (IDM) and no majority attitudes or opinions have surfaced in the general public. Methods: This study reviewed the current literature on IDM and attitudes in PGT by searching key terms in the CINHAL, Medline and PsychINFO databases. Initial review returned a total of 689 articles on these two topics. Further review and exclusion based on language, content and year of publication led to a reduction in the total number of articles to approximately 31 included in this review. The results of the review were then used to discuss future research studies. Results: Studies show that much remains to be done in the research. There are many gaps in the literature. Overall, no consensus exists in the limited articles in publication. This review shows that individuals want to have autonomy and make their own decisions; however, little over half actually make these decisions with adequate information. Conclusions: Using the literature provided, the researcher proposes a 3-instrument questionnaire designed at eliminating the gaps discussed once finished. The instruments range from IDM tools to attitude assessments.
EUTHANASIA: PERCEPTIONS AND ETHICAL CONSIDERATIONS OF DOCTORS IN PAKISTAN.
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BACKGROUND: The present era has witnessed tremendous improvement in palliative care which has intensified the debate of euthanasia. Being Islamic republic, its practice is not legalized in here but it is the necessity of time that the perspective of doctors in Pakistan should be evaluated. OBJECTIVE: The purpose of this study is to know the perception and the ethical concerns of doctors towards euthanasia in Pakistan. METHODS: It was a cross-sectional study conducted from August 2008 to February 2009 in three major government hospitals of Karachi. Ethical review board approval was taken prior to the commencement of the study and only those doctors who consented to participate were interviewed through a pre tested interviewer administered questionnaire. To carry out data entry and statistical analysis SPSS-12.0 was used. RESULTS: Out of 248 doctors approached 153 consented to participate in the study. The male to female ratio was 90:63 and the mean age was 30.90 with ± 6.580. It was quite interesting that only 89 doctors knew about euthanasia therefore the remaining results were out of them: Regarding different types of euthanasia used 69.66% of the respondents were aware of voluntary euthanasia. Law of Pakistan about the euthanasia was known to 53.93%. About the ethical considerations only 25.84% of the doctors believed that it is ethical to practice euthanasia on a patient. During practice 22% of doctors were encountered in a situation where their opinion was taken about the practice of euthanasia and 60% of them had advised it. CONCLUSION: It is quite astonishing that more than a third of the doctors in Pakistan did not even know about euthanasia and only one fourth of those who knew about it believed that it is ethical to practice. However, since it is an important issue in the care of terminally ill patients, our health professionals are in favor of further research of this controversial, yet debatable issue for the benefit of our society.

ENACTING LEGISLATION TO RESTRICT YOUTH ACCESS TO TANNING BEDS: A SURVEY OF ADVOCATES AND SPONSORING LEGISLATORS
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Background: There is a strong correlation between ultraviolet exposure via tanning bed use before age 35 and malignant melanoma and squamous cell cancer, and a 75% increase in melanoma risk when a tanning bed is used before age 30. Increased risk of skin cancer with younger age of exposure to tanning booths has led to recent legislative efforts to protect minors. Many states only require parental consent, which has no impact on decreasing the prevalence of youth tanning bed use. Passing tanning bed legislation restricting underage use has remained challenging. Objective: Our goal was to determine the resources required to pass future tanning bed legislation and identify current key barriers to the enactment of these laws. Methods: 15 states sought to pass tanning bed legislation in 2006; in-depth surveys were created and completed with advocates in 10 states and legislators in 5 states. Results: Advocates sought advice from the sponsoring legislator(s) (n=9), held discussions with other organizations (n=8), and used a lobbyist (n=5). The three major barriers for advocates were strong lobbying efforts by the tanning bed industry (n=10), legislative proceedings after the bill was filed (n=5), and obtaining support from other organizations (n=4). For legislators, the most significant barrier was making colleagues aware of the health effects of tanning bed use. Conclusion: Legislation to restrict youth access to tanning beds has been attempted in several states. States that impose age restrictions on tanning bed use are more effective than states requiring parental consent in decreasing the prevalence of tanning bed use among youth. Herein, we found that successful advocates collaborated with local and national organizations, and enlisted lobbyists who had direct contact with the sponsoring legislator and strongly aided the passage of the bill. Collaboration with multiple and diverse sources can increase the chance of successful passage of legislation. Since all advocates reported that the tanning bed industry was the most significant barrier in passing legislation, a description of industry and counter-industry arguments should be made available on all advocacy web sites. Supporting legislators should have access to research data detailing the hazards of tanning bed use. Lessons learned from this pilot survey of advocates and legislators and larger ones to follow can pave the way for planning of new campaigns to restrict tanning bed use by minors.
Poster 19
PERSONALITY TYPES OF OTOLARYNGOLOGY RESIDENT APPLICANTS AS DESCRIBED BY THE MYERS-BRIGGS TYPE INDICATOR (MBTI)
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Background: The Myers-Briggs Type Indicator (MBTI) has been used for decades for assessing individual personality types and characterizing groups of people. To our knowledge, there is no published study that examines the personality types of otolaryngology residency applicants as described by the MBTI, despite the personality trends for ‘typical’ otolaryngologists. Objective: To assess the personality profiles of prospective applicants to a single otolaryngology–head and neck surgery residency program using the MBTI. The personality types of these individuals were compared to those of the general population and to physicians in other medical specialties. Methods: This cross-sectional survey included an anonymous MBTI survey, which was emailed to 154 resident physician applicants in spreadsheet format. Analysis of the completed surveys was accomplished through calculating the prevalence estimates and p-values. Results: Of the 154 anonymous surveys, 86 were completed (response rate 56%); the ESTJ personality type was the most prevalent (14%) which represents 13% of the general population. Prospective applicants displayed mostly extroverted (53%), sensing (54%), thinking (60%), and judging (65%) personality traits. Statistically significant differences were found between otolaryngology resident applicants and the general population for the INTJ (p=.032), ISTJ (p=.035), and ESFP (p=.003) personality types. The most common statistically significant personality type was ISTJ (13%), while the least common was ESFP (1.2%). The intuitive, (47%) and perceptive, P, (35%) types correlated closely with the personality types of those individuals in non-primary care specialties (47%) and surgical specialties (28%). Extraverted and thinking individuals appeared to prefer surgical specialties, which occurred in 51% and 59% of the applicants, respectively. Conclusion: This study is the first study of its size examining the personality types of medical students applying to an otolaryngology residency. The prevalence of intuitive and perceiving personalities matched closely with other surgical fields. There were also significant differences between the prevalence of certain personality types in our applicant pool and the general population. These results may allow for a better understanding of the personalities of medical students who are interested in otolaryngology.

Poster 20
FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN OMAN: FROM NON-EXISTENCE TO MOLECULAR CHARACTERIZATION.
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Background and Objectives: Familial Hemophagocytic lymphohistiocytosis (FHLH) is an autosomal recessive disorder typically occurring in infancy, characterized by fever and hepatosplenomegaly associated with pancytopenia, hypertriglyceridemia and hypofibrinogenemia. We report the outcome of FHLH in a developing country, with regard to clinical, laboratory and genetic features. Methods: A nation-wide study on all patients diagnosed with FHLH in Oman during the 12-year period 1997-2009 was performed. Results: Before 1997 no single case was identified in Oman, and in 12 years we are now able to diagnose this disease independently on the genetic level. Thirty patients with FHLH were identified, 16 (53.3%) of whom, had clinical manifestations of central nervous system involvement at presentation. In none of the patients an infectious cause could be identified. Nineteen (63.3%) children died; 13 (43.3%) were referred late in the disease course, and the concern about starting chemotherapy before exclusion of an acute infection resulted in delayed treatment in some patients. Three (10%) children were started early on the HLH-94-therapy followed by BMT. Eight (26.6%) children were started on HLH-2004 protocol, and four (13.3%) of them were successfully transplanted. Genetic mutations were identified in all the patients. Conclusions: We report our incidence, clinical characteristics, and treatment outcome of FHLH in Oman.
Poster 21
PAIN IS ASSOCIATED WITH MORTALITY IN HEMODIALYSIS PATIENTS
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Objective: Patients' perception of pain during dialysis (HD) and exclusive of HD treatment and its association with survival have not been well studied in end-stage renal disease (ESRD). We evaluated the experience of pain during HD and at times the patient was not receiving HD and assessed possible associations of perception of pain and sleep disturbance with patient survival. Methods: 128 ESRD patients treated with HD completed questionnaires on psychosocial status, quality of life, and sleep disorders. A modified McGill Pain questionnaire was used to assess the nature, location, frequency, intensity and duration of pain both during and exclusive of HD. The Pittsburgh Sleep Quality Index was used to screen for sleep disturbances over a 30 d period. Results: Controlling for age, diabetes mellitus, serum albumin concentration, and HIV infection, there was a significant association between mortality and both frequency (HR = 1.097, CI = 1.001-1.201, p = 0.047) and intensity of pain while patients were not on HD (HR = 1.090, CI = 1.001-1.187, p = 0.047). There was no association between survival and duration of pain off HD or any of the pain parameters while patients were on HD. There was no association between survival and the presence of a sleep disorder. Conclusions: Pain perception off HD may be of more importance to patients than pain during HD. The mechanisms underlying the association are unknown, but may involve linkage of pain with severity of medical illness, or the generation of a maladaptive cytokine response. Multicenter prospective studies of pain interventions using well-validated pain perception tools are needed to establish causal relationships. Interventions directed towards treating pain on non-HD days may improve ESRD patient survival.

Poster 22
INTERFERON REGULATORY FACTOR 6 GENE MUTATIONS IN NON-SYNDROMIC CLEFT LIP AND PALATE IN THE HONDURAN POPULATION.
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Cleft lip with or without cleft palate (CLP) and isolated cleft palate (CPI) are common congenital malformations, occurring in 1.5-2 per 1,000 Caucasian births, with greater prevalence in Hispanic, Asian, and Native American populations (1 per 500). Clefting abnormalities are associated with increased morbidity and mortality in infancy, childhood, and adulthood. Both environmental and genetic factors cause CLP and CPI. Environmental factors include maternal smoking, folate deficiency, and the use of steroids, anticonvulsants, or methotrexate during pregnancy. Up to 50% of CPI and 30% of CLP are syndromic cases associated with congenital defects of other organ systems, with chromosomal abnormalities that often follow Mendelian patterns of inheritance. Non-syndromic forms of CLP have indeterminate inheritance patterns, reduced penetrance, and positive family histories in only 33% of affected patients. In previous work, an association was found between interferon regulatory factor 6 (IRF6) and non-syndromic CLP in the Honduran population. The Honduran population is well suited for genetics evaluation because it remains fairly genetically homogeneous and has a high incidence of CLP. To reduce environmental contributions, we restricted analysis to families with non-sporadic cases (two or more members affected) of non-syndromic CLP. Current work by our group involves determining if specific mutations exist in our study population of non-syndromic cases of CLP by sequencing the IRF6 gene, which is composed of 9 exons (7 coding and 2 non-coding regions). Polymerase chain reactions were carried out to amplify exons 1-9 of 87 probands, and subsequent gene sequencing was performed. 23% of the probands had at least one base pair change in or around exon 1. 72% of the probads had a C to G base pair change at base pair 93 within exon 8. In future work, to determine if a gene mutation in IRF6 is related to nonsyndromic CLP and not merely population based, the IRF6 gene in non-affected control subjects will need to be sequenced. Our preliminary results further support the growing body of literature emphasizing the importance of IRF6 in the development of CLP.
Poster 23

KNOWLEDGE, ATTITUDES & PRACTICES (KAP) OF GENERAL PRACTITIONERS REGARDING SEXUALLY TRANSMITTED DISEASES (STD’S) AND HIV/AIDS IN KARACHI, PAKISTAN.

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BACKGROUND: In Pakistan the morbidity and mortality due to STDs is significantly increasing. Karachi is the largest city of Pakistan and most of the cases of STDs here are treated in private clinic settings.

OBJECTIVE: To assess the Knowledge, Attitudes and Practices of general medical practitioners of Karachi regarding STDs and HIV/AIDS. MATERIALS & METHODS: This is a cross sectional survey carried out in Karachi, Pakistan. Sampling frame included general practitioners from different towns with appropriate qualification (at least MBBS). WHO Protocol for Control of Sexually Transmitted Diseases was used to develop the KAP questionnaire. Trained interviewers used a pre-tested questionnaire for individual interview. Microsoft Access 2002 was used for data entry and SPSS 12.0 is used to carry out the Statistical analyses. RESULTS: Out of 176 doctors approached 103 consented to participate in the study. Among 103 general practitioners 86 were males and 17 were females, the mean age was 35.22 years with ± 10.70. Regarding the organisms transmitted through sexual intercourse 93.2% knew about Neisseria gonorrhoea, 80.6% for Hepatitis B virus, 70.9% for Herpes Simplex-2 virus, 60.2% for Human Papilloma Virus (HPV) and only 25.2% for Haemophilus ducreyi. About transmission routes of HIV the response was 100%, 97.1%, 99%, 91.3%, 97.1% & 48.5% for homosexual contact, heterosexual contact, blood transfusion, mother to fetus, sharing needles & breast feeding respectively. Only 26.2% heard about WHO syndromic management of STDs. 74.8% thought that STDs patients were threat to the community, on question how to treat a HIV positive patient only 40.8% said they will refer to AIDS control program. Sixty three percent of GPs have seen STDs patients in their practice out of which 94.2% knew the value of sexual history but only 55.3% were aware of recommended treatment regimen. CONCLUSION: Knowledge, Attitudes & Practices of doctors has found to be reasonably well overall but a lot of improvement has to be done to deal with this important issue particularly in our country where level of awareness is low and risk groups of HIV & STDs exists. Targeted continuing medical education (CME) programs are recommended.

Poster 24

BREAST CANCER SCREENING IN WOMEN WITH DISABILITIES

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Background: The U.S. Surgeon General recommends eliminating health disparities for people with disabilities to promote their independence particularly now with longer life expectancies increasing their need for preventive services. One of the focus areas of Healthy People 2010 was to increase the use of effective screening tests. Research prior to 1997 demonstrated that Medicare beneficiaries with disability, including women with mobility limitations, such as, difficulty standing, walking, or climbing stairs, were less likely to receive a mammography. We would like to assess the barriers to screening mammography encountered by women with disabilities. Objective: To assess the reasons older women with disabilities are less likely to receive a screening mammography than women without disabilities. Methods: We selected a cohort from Medicare Current Beneficiary Survey 2004 – 2005, limiting the study to women who were 65 years or older. The women were stratified by level of disability and by age. Reasons reported for not having mammography were calculated from the survey with a standard error. Results: Reasons reported by women with moderate and severe disabilities for not receiving mammography were the following: the doctor did not recommend it, there was no need, they forgot it, they reported pain, illness or lack of transportation. Conclusion: The likelihood of mammography decreases with a severe level of disability. Barriers encountered by women with disability included forgetting it and transportation problems whereas other issues were illness, no need for the test or a physician not recommending it. Future studies are needed to compare mortality risks in those that received the mammography to those who did not.
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TOWARD AN IMPROVED UNDERSTANDING OF CAUSES OF THE AUTISM SPECTRUM DISORDERS: APPLICATION OF A NOVEL SYSTEM FOR EVALUATING GENETIC AND METABOLIC DISEASE PROCESSES IN CAUSATION OF AUTISM
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Background: The Autism Spectrum Disorders (ASDs) are among the most common disorders in pediatric medicine, affecting an estimated 1 out of every 110 children. The high prevalence and considerable associated morbidity make an understanding of the causes and treatment of ASDs a national medical priority. While studies have demonstrated a genetic basis for the ASDs, an underlying etiology is determined for only a minority of patients (<20%). Many have hypothesized that ASD is often a multifactorially-determined condition; however, there are no published cases of multifactorial ASD. Surprisingly, there are also no published criteria for defining an etiology of ASD. Methods: We reviewed medical records of 111 consecutive patients seen in our clinic since 2006 who met DSM-IV criteria for ASD and who had undergone comprehensive genetic and metabolic evaluation. Based on advances in clinical, biochemical, chromosomal and molecular genetics, we also designed a criteria system for defining when a genetic or metabolic condition is definitely, probably or possibly contributory to causation of ASD. We then applied the criteria to the subjects in our study. Results: Based on this patient population, definite, probable and possible contributory etiologies of ASD were determined for 12%, 7% and 11% of the patients, respectively. Of those classified as definite or probable, 6 % had chromosomal lesions, 3 had mutationally-defined monogenic disorders, 7 had mitochondrial cytopathies and 1 had a syndromic diagnosis. One patient had multifactorial autism with both a chromosomal lesion and a single gene disorder of SCN1A and one sib pair had two nonallelic, heterozygous mutations of fatty acid oxidation. Factor analysis revealed that both craniofacial dysmorphism and significant non-CNS organ system anomaly/dysfunction were patient characteristics that were significant for predicting discovery of a definite or probable contributory etiology. Conclusions: This study is the first to create a criteria system for defining when and to what degree a genetic or metabolic condition is contributory to causation of ASD. Such a system is important for the advancement of our understanding of diagnoses and pathogenesis of the ASDs. Based on these criteria, we found definite or probable contributory etiologies in 19% of our patients, including some heretofore unappreciated etiologies. In addition, this study describes the first proven cases of multifactorial ASD.

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WALL SHEAR STRESS AT THE CAROTID TERMINUS AND SURROUNDING SEGMENTS ASSESSED VIA VELOCITY-ENCODED HIGH-SPEED PHASE-CONTRAST MAGNETIC RESONANCE ANGIOGRAPHY AND AUTOMATED SPLINE INTERPOLATION
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Introduction: Complications of atherosclerosis are the leading cause of death in industrialized countries; convincing data has emerged suggesting that abnormally low wall shear stress (WSS) is prevalent at atherosclerosis-prone sites. WSS analysis may have prognostic value in finding areas vulnerable to plaque formation and progression. A limitation of prior investigations of WSS using magnetic resonance angiography (MRA) is lack of sufficient spatial resolution necessary to visualize the boundary zone (BZ) within clinically-useful scan times. We have developed PC-VIPR, a 3D-radial MRA technique capable of acquiring whole-brain angiograms with scan times of ~5 minutes and spatial resolution more than 40 times higher than conventional techniques, allowing better boundary zone visualization. In this study, we examine WSS at the carotid terminus and surrounding segments in 10 volunteers. Materials & Methods: 10 healthy volunteers (6 female, 4 male) were scanned using a GE Discovery 750 3.0T MR Scanner with 8 channel head coil using PC-VIPR. The images were imported into Ensight where cutplanes axial to the vessels of interest were made. Using spline interpolation, points were selected around each vessel on magnitude images to create axial spline ROIs for each timepoint; the software then calculated time-average WSS from PC-VIPR velocity measurements. Results: The time average WSS for all subjects in the proximal left/right MCAs were 1.09 ± 0.42 Pa. The WSS in the proximal ACAs were 0.89 ± 0.59 Pa, the WSS in the terminal ICAs were 1.17 ± 0.60 Pa, and the WSS in the carotid termini were 0.36 ± 0.10 Pa. These values are consistent with values found in the literature for WSS measured with PC-MRA. Discussion: Previously, the calculation of WSS with MR has been limited by insufficient resolution for BZ visualization and difficulty in BZ localization. The combination of PC-VIPR and automated spline interpolation is a tool that can localize the BZ and can calculate velocity, volume flow rate, and WSS in vessels of interest with total processing time of 15 minutes per vessel. We are currently performing scans on patients with atherosclerotic stenoses and using normal values from this study as a baseline for comparison. We anticipate that by combining WSS and velocity measurements with morphology acquired using PC-VIPR, patients at risk of atherosclerotic progression, transient ischemic attacks, and ischemic strokes can be identified quickly and non-invasively.

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SNR REQUIREMENTS FOR ACCURATE POST-CONTRACTION SIGNAL ESTIMATIONS
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The amplitude of the post-isometric contraction signal intensity change (ΔSI) in dynamically acquired magnetic resonance (MR) images may reflect muscle microvascular function. ΔSI may be lower in diseased populations; however, the image parameters required for accurate quantification of ΔSI are not known. The purpose of this study was to use in vivo and simulation data to determine the minimum signal-to-noise ratio (SNR) requirements for accurate ΔSI quantification. One subject completed six series of single 10s maximum voluntary isometric dorsiflexions. A set of 150 images was dynamically acquired using a dual gradient echo sequence with TR/TE=100/6, 46ms. SNR was varied by acquiring different slice thicknesses (2, 4, 10mm) for each series. The mean ΔSI and SNR for each TE (SI6 and SI46) were computed in the deep tibialis anterior. The highest SNR in the in vivo trials was defined as the initial signal for simulations. To examine the accuracy at lower ΔSI, signal amplitude was reduced to 25, 50, and 75% of the initial value. 2000 realizations of Rician noise were generated for each ΔSI and TE value, at each of twenty SNR’s. ΔSI was overestimated in SI6 in vivo data until SNR reached a minimum of 150, while the SI46 in vivo estimation did not change with SNR. In simulation data, the mean ΔSI was overestimated until SI6 and SNR was >250 and >120 respectively, independent of changes in ΔSI. Together, the simulation and in vivo results provide SNR minima for design and interpretation of future studies.

AUTOMATED IMAGE ANALYSIS OF ESTROGEN RECEPTOR IMMUNOMARKERS IN BREAST CANCER
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The aim of this study was to evaluate the clinical utility of automated analysis of estrogen receptor immunohistochemical staining in breast cancer as a potential validating platform for new candidate antibodies with similar staining pattern. Tissue microarrays containing 275 clinical breast carcinomas were used; immunohistochemical stainings for estrogen receptor (ER) was done and slides digitalized by ARIOL (Applied Imaging Inc, USA) system. Pathologists scored the images semi-quantitatively in order to obtain the standard for training of automated algorithms using the Allred scoring method. The images were analyzed and scored using customized algorithms developed using the MATLAB (Natick, USA) software platform. The algorithm used a color deconvolution technique to separate the stain colors and used a marker based watershed algorithm to segment cells from other cells and from the background. A linear discriminant was used to classify the individual cells based on their staining intensities. ROC analysis was used to define the optimal sensitivity and specificity cut-off once the algorithm was optimized. The cut-off for a positive case by automated analysis was greater than 6.5% positive nuclei. There were 74.2% ER positive and 25.8% ER negative by automated analysis, compared to pathologist’s 77.8% positive and 22.2% negative. There were 1.1% false positive and 4.7% false negative automated results. The false positive results were due to the variable background staining while the false negative results were caused by very low intensity staining level. Overall there was consistently high agreement between manual pathologist and automated scores; the automated ER scoring reached 94 % sensitivity and 95 % specificity and a kappa of 0.8 (high agreement). Thus, automated digital image analysis of nuclear immunomarkers in breast cancer is a sensitive and specific analytical tool; this approach can be applied to the automated morphological screening of novel candidate antibodies with a nuclear staining pattern in translational research settings.
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VOLUMETRIC MRI MEASUREMENTS OF GLIOBLASTOMA MULTIFORME TO PREDICT DIRECTIONAL TUMOR PROGRESSION: MODIFICATION AND VALIDATION OF 3D GLIOMA GROWTH MODEL
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Purpose: Glioblastoma multiforme (GBM) are the most aggressive primary brain tumors. The treatment of GBMs is hindered by the rapidly growing and highly invasive nature of the tumor. Our previous mathematical model demonstrated that the tumor expansion and invasion could be predicted with techniques used commonly in weather forecasting. This project seeks to incorporate Magnetic Resonance Imaging (MRI) characteristics to modify the existing model as well as provide the individual patient neuroanatomy as the framework on which the model algorithm is run for greater accuracy in predicting tumor growth and recurrence. Materials and Methods: Retrospective volumetric analysis of 15 glioblastoma multiforme patients was performed using MIPAV software. Contrast enhancement and tumor volume were measured from T1 MRI images and edema volume was obtained from T2 MRI images obtained during the entire course of treatment for each patient. Measurements from ten patients provide a calibration tool for the mathematical model. Growth characteristics of the tumor were gathered from the rate of change of MRI image volumes. MATLAB software was used to convert patient MRI DICOM images into gray and white matter binary images. Results: Changes in the T1 weighted MRI image contrast enhancement closely matched the tumor growth rate for the 15 patients. Edema rate of change measurements did not match well with tumor growth and does not allow prediction of tumor growth rate. Patient MRI images were easily converted into gray and white matter binary maps for the mathematical model to utilize. Conclusions and Future Work: Contrast enhancement imaging changes closely match glioblastoma growth rates and provide additional parameterization in determining the tumor growth rate differential equation of the mathematical model. Edema growth rates, the other important and common imaging characteristics, do not help predict growth rates of tumors. Future work involves calibrating the mathematical model using the first 10 patients while using the binary patient brain map. Additional analysis of directional growth will be performed by looking at contrast and edema characteristics with respect to new tumor growth foci. Finally, the mathematical model will be validated using volumetric measurement from 30 patients.

Poster 30
THE UTILITY OF COMPUTED TOMOGRAPHY SURVEILLANCE FOR PRIMARY SITE RECURRENCE OF SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK
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Background: Even with the advancement of the primary treatment options for squamous cell carcinoma (SCC) of the upper aerodigestive, treatment failures and recurrences still occur. Local recurrence rates have been reported by various groups and range from 10-54%. Follow up methods for monitoring these patients for recurrence include physical examination (PE) as well as radiologic imaging techniques, such as computed tomography (CT). In recent reports, the sensitivity and specificity of CT in the detection of recurrent SCC in the upper aerodigestive tract have varied widely. Sensitivities ranged from 53 to 83% while specificities ranged from 59 to 95%. However, none of these studies directly compared the utility of CT with that of PE in detecting primary site recurrences. Objectives: The utility of CT scans in evaluating neck node metastasis has been shown. This study aims to evaluate the utility of CT compared to PE in evaluating primary site recurrences. Methods: A retrospective cohort study was conducted. Patients who received both CT scans and PE after primary treatment for squamous cell carcinoma of the upper aerodigestive tract (oropharynx, hypopharynx, and larynx) were identified. Each individual CT scan and PE was evaluated for its ability to detect a patient’s recurrence status. Positive test results were compared to subsequent biopsy results to determine their validity. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each test. Recurrence rate and mortality were calculated for each site and the entire group. Results: 131 patients underwent a total of 886 PE and 346 CT scans during the 2 year follow-up. The overall recurrence rate was 26.7%. The recurrence rate by site was 40.5% for larynx, 16.6% for hypopharynx and 18.3% for oropharynx. The sensitivity for PE and CT was 84.0% and 66.7%; for specificity, 98.7% and 90.7%; for PPV, 65.6% and 31.8%; for NPV the values were 99.5% and 97.7% respectively. Conclusions: Due to the low sensitivity and PPV of CT scans compared to physical examination in evaluating primary site tumor recurrences, the utility of computed tomography for surveillance may be limited.
Introduction: Gadolinium chelates, the major group of contrast agents used in magnetic resonance imaging (MRI), have been recently implicated as the cause of nephrogenic systemic fibrosis (NSF), a potentially fatal systemic disease. Agents with linear structures, like gadodiamide, are responsible for the majority of worldwide cases, whereas no macrocyclic agent has been directly linked to NSF. The greater stability of the latter agents leads to substantially reduced in vivo dechelation and reduced subsequent deposition of toxic gadolinium ions into body tissue. Purpose: This study aims to evaluate a promising macrocyclic agent currently in US clinical trials, gadobutrol (Gadovist), in comparison to gadodiamide with regard to lesion enhancement in a rat brain glioma model. In addition, the possibility of dose reduction with gadobutrol at higher field strengths (3 T) is examined. Methods: Glioma cells were injected into the brains of 54 live rats which were divided into three groups. Groups 1 and 2 were randomly administered equivalent doses (0.1 mmol/kg) of gadodiamide and gadobutrol 24 hours apart. Following each injection, group 1 animals were scanned at 3 T and group 2 animals at 1.5 T. Group 3 animals were administered full or half-dose gadobutrol and scanned at 1.5 and 3 T, respectively. T1-weighted images were analyzed pre-contrast and at five time points post-contrast with respect to signal- and contrast-to-noise ratio (SNR, CNR) and contrast enhancement (CE). Results: At 3 T improvements in SNR, CNR, and CE with gadobutrol ranged from 11.8-16.0%, 30.5-35.4%, and 27.1-31.5%, respectively, and at 1.5 T from 7.0-11.1%, 27.1-35.8%, and 23.8-29.5%, respectively. Differences between these parameters with gadobutrol and gadodiamide were statistically significant (p<0.0001 to 0.05) at all times following contrast administration. In group 3, no significant difference (0.3<p<0.7) in CNR or CE was found between full dose gadobutrol at 1.5 T and half-dose at 3 T. Conclusions: This study demonstrates improved lesion enhancement with gadobutrol versus gadodiamide. To date no macrocyclic agent, like gadobutrol, has been directly associated with NSF. This, in combination with the demonstrated superior lesion enhancement, makes gadobutrol a safe, effective choice for contrast enhanced MRI. Furthermore, efficacious imaging with half-dose gadobutrol at 3 T offers both a reduction in theoretical risk (for NSF) and potential cost savings.

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THE EFFECT OF OSTEOCHONDRAL DEFECT SIZE ON RIM STRESS AND REDISTRIBUTION OF LOAD IN THE TALUS
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Background: Osteochondral lesions of the talus (OLTs) are common causes of ankle pain and disability. Operative treatment of these lesions focuses on excision with curettage and drilling (ECD), which relies on ingrowth of biomechanically inferior fibrocartilage, or some type of hyaline cartilage surface restoration (osteochondral grafting). Current guidelines favor osteochondral grafting for “larger lesions” or those lesions that have failed ECD. However, to our knowledge, there is no biomechanical support for determining at what size lesion treatment should consist of ECD versus osteochondral grafting in the talus. Objective: The purpose of this study was to determine the effect of osteochondral defect size on rim stress concentration, peak rim stress, and redistribution of load to adjacent areas of the talus after the creation of posteromedial OLTs. We sought to determine if a critical defect size exists, in which adjacent cartilage may be damaged with loading, and therefore may benefit from osteochondral grafting rather than ECD. Methods: We made OCDs in the posternomedial region of the talus using an Arthrex OATS (osteochondral allograft transplantation system) coring device in eight fresh frozen below knee amputations. We then used an MTS load cell to load the cadaveric ankles with 700N, simulating the pressure involved in typical walking. A Tekscan digital electronic pressure sensor recorded the pressures inside the tibiotalar joint and the distribution of pressure around the artificial OCD. Results: We found a statistically significant increase in rim stress concentration and peak rim stress with OCDs greater than 1cm^2 when compared to no OCD (p<0.05). In addition, we found that there was a distinct redistribution of load in the talus when OCDs became 1cm^2 in size, which was not seen with smaller OCD sizes. Conclusions: This study shows that OCDs 1cm^2 or greater cause a significant increase in rim stress concentration and peak rim stress, as well as causing redistribution of load in the talus. In light of these findings, it seems that 1cm^2 is the critical defect size that should be considered when deciding between ECD versus osteochondral grafting for a patient with an OCD of the talus. Based on this study, patients with an OCD of 1cm^2 or greater should undergo osteochondral grafting instead of ECD because the fibrocartilage produced in ECD might be damaged by the increased rim stress and load redistribution caused by an OCD of that size.
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HEAD AND SPINE INJURIES IN ROLLOVER CRASHES
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Background: Almost 3 percent of all vehicle crashes in the US are rollover crashes. However, rollover crashes make up almost 28 percent of all fatal crashes. Severe or lethal head, brain, and spine injuries make up a large portion of all the injuries in rollovers. Objective: To identify the most frequent head and spine injury patterns during rollover crashes in the CIREN database based on different factors. Methods: The subjects were categorized into two groups of near sided and far sided rollovers (occupant being seated near to or far from the side leading into the roll) and furthermore into smaller 20-degree groups based on each subject's yaw angle (the displaced amount of rotational angle from direction headed right before rolling). For each group of near sided and far sided rollovers, the pattern of head and spine injuries were observed and analyzed based on the yaw angles and vehicle types. Results: The data shows the severity of injuries in rollover crashes as predicted. Compared to near sided rollovers, the far sided rollovers received more severe injuries. Vehicle type also seems to affect the injuries. More than 80% of subjects in cars in near sided cases had MAIS 3 or higher compared to 41% of all near sided and 17% of near sided SUV cases. Subsequently, near sided car cases had higher percentage of cases with surgeries and MAIS 4 or higher injuries. On the other hand, there is no significant difference between severity of injuries received by occupants of cars and SUVs in far sided cases. However, 75% of all cases in far sided rollovers had MAIS 3 or higher injuries, which is significantly greater than the 41% in near sided crashes. Among all vehicle occupants needing surgery, 60% of near sided cases and 67% of far sided cases had at least one fracture in either the anterior (body) or posterior column (lamina, pedicle, or facet) of C6 or C7. With regards to yaw angles at rollover, various trends have been observed such as: 75% of cases with spinal process fractures are between 45 and 60 degrees in near sided and between 90 and 130 degrees in far sided crashes; 67% of near sided cases with C1 fractures are between 45 and 60 degrees while 100% of far sided cases with this type of fracture are between 120 and 130 degrees; etc. Conclusions: The cases with far sided rollovers had more serious injuries while car occupants received significantly more severe injuries in near sided rollovers. Yaw angles can additionally be used as predictor of injuries.

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METABOLIC CHANGES FOLLOWING SURGICAL RESECTION OF PITUITARY TUMORS CAUSING ACROMEGALY
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Background: Excess growth hormone and elevated levels of IGF-1 have been associated with increased body weight, decreased body fat mass, hypertension, cardiovascular disease, and insulin resistance. The changes in various parameters ensuing postoperatively are of interest, particularly in relation to whether the patient enters remission following surgery. Methods: Patients presenting to the CUMC for surgical treatment of acromegaly over the past five years were included in the study. Those patients who could not be followed for 6 months postoperatively were excluded. Patients presented for a preoperative visit and appointments at 1 month, 3 months and 6 months postoperatively and henceforth annually. They were categorized as active or in remission based on the normalization of IGF-1 levels by 6 months postoperatively. Statistical comparisons between the groups were based on the student's unpaired t-test with Welch's correction utilizing the Prism software. Results: Eleven active patients and 21 in remission were included in the study. Active patients had a mean baseline IRA-GH value of 31.42 ug/L and a final mean value of 3.61 ug/L, while patients ultimately categorized as achieving remission had a mean baseline value of 17.5 ug/L and a final mean value of 0.44 ug/L. There was no statistical difference between the means at baseline; however, the final averages differed significantly (p= 0.0436). Members of the remission group demonstrated significantly greater increases in ghrelin from baseline (149.1 pg/mL) than did the active group (61.44 pg/mL) (p=0.0054), and also achieved significantly higher % ghrelin suppression as compared with the active group (p=0.0422). While the calculated Quick-i values, an indirect measure of insulin sensitivity, increased in both groups, the increase was significantly greater among patients in the remission group (p=0.035). Changes in weight over the course of the study significantly differed between groups (p=0.0190); active patients lost an average of 1.173 kg over the course of the study while patients in remission gained on average of 2.817 kg. Changes in systolic and diastolic blood pressure, CRP and leptin levels did not differ significantly between groups. Conclusions: Changes in physiological parameters, particularly weight, insulin sensitivity and ghrelin, following surgical treatment for acromegaly differ significantly in magnitude depending upon whether remission is attained.
OUTCOMES OF INTERNAL FIXATION OF FRACTURES OF THE FEMORAL NECK
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BACKGROUND: In elderly age patients mortality rate following a hip fracture is 20%-35% within a year, of which 80% are women. For its fixation different procedures have been described in literature. Fracture fixation with cannulated screws seems to be a valid option with the preservation of the patients own femoral head and limited incidence of reoperation in the future. Long term complications of this procedure include non-union of the fracture and avascular necrosis of the femoral head. OBJECTIVE: To determine the outcome of internal fixation for fractures of the femoral neck. METHODS: This was a retrospective case series conducted by reviewing the medical records and x-rays of patients visited Aga Khan Hospital, Karachi with femoral neck fracture from the year 1999-2009. Coding used was fracture neck of femur. Only those patients who had a complete medical record and had no other intervention done along with fixation of the femoral neck were included in the study. SPSS 12.0 was used to carry out the data entry and statistical analyses. RESULTS: Out of total 77 patients included 45 were males and 32 were females and the mean age was 49.65 years ± 18.88. Minimum follow up was at least 1 year. The etiology of fractures was fall (80.5%), gun shot (2.6%) and RTA (16.9%). On the basis of Garden’s classification of femoral neck fractures 30% were of type 1, 28.6% were of type 2, 17% were of type 3 and 24% were of type 4. Outcome was assessed by evaluating clinical and radiological outcome for healing, non-union and avascular necrosis of the femoral head. Non-union developed in only 3 patients with avascular necrosis in 11.7% of the patients. The healing time was 9-12 weeks in 44% of the cases. CONCLUSION Fixation with cannulated screws of femoral neck fractures appears to be a successful procedure in young and relatively old high demand patients. In majority of cases patient’s own hip was preserved. Patients with AVN of the femoral head also remained asymptomatic and went on to healing.

STERNAL WOUND INFECTION AS A POST OPERATIVE COMPLICATION AFTER OPEN HEART SURGERY: PREVENTION AND TREATMENT
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BACKGROUND: Elderly patients undergoing cardiac surgery have high rates of post operative morbidity and mortality rates. Rate of incidence of deep wound infections after cardiac surgery is 0.4%-5% with a mortality rate of 8%-80%. Management is mainly done through surgical procedures. Usage of honey after surgeries for its antimicrobial & wound healing properties has also been reported OBJECTIVE: Our objective is to assess the prevention and treatment of sternal wound infections developed after open heart surgery. MATERIALS & METHOD: It is a retrospective study conducted by the collection of data from medical records of referred patients treated privately in Karachi with the case of any sternal wound infection occurring as a complication after open heart surgery from the year 2006 to 2007. Patients younger than 50 years of age are excluded from the study. SPSS 12.0 is used for data entry and analysis. RESULTS: Total 53 cases of post operative sternal wound infection were reviewed, out of them 37 were included in the study and 16 were excluded on the basis of age. Among the 37 cases included the male to female ratio was 34:3 and the mean age was 57.2 with ± 4.88. Considered risk factors have shown significant associations with the development of sternal wound infection as 33 (89%) patients were known case of diabetes and in all cases internal mammary artery was used as a bypass graft. Time of presentation of sternal infection after cardiac surgery was 4-6 weeks in 24 (65%) cases. In 68% of the cases only sternal wire was infected whereas 32% were of osteomyelitis & osteochondritis along with infected sternal wire. The treatment of all the cases performed surgically through sternal wire removal, costo-cartilage resection & debridement followed by daily dressing & usage of honey after 2 weeks. Antibiotics based on blood culture were given for at least 2 weeks. All the cases were treated successfully & have no other complications up till 3 months follow up. CONCLUSION: Our research showed that risk factors like diabetes, smoking, rethoracotomy & usage of internal mammary artery have significant role in developing sternal wound infections after cardiac surgery. Usage of honey in the treatment plan has shown a significant result.
A CROSS-SECTIONAL COMPARISON OF CLEFT LIP SEVERITY IN THREE REGIONAL POPULATIONS
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BACKGROUND: Cleft lips are congenital defects that occur in early embryonic development. While one out of 800 children in the United States is born with a cleft lip or palate, developing countries show a markedly higher incidence of one in every 500 births. A global pattern of cleft lip severity has not been previously assessed. Operation Smile, a global children’s medical charity, coordinated the “World Journey of Smiles” in November 2007 to surgically repair 4,149 facial deformities in 25 countries. Medical photographs of consenting patients offer insight into phenotypic differences in cleft lip severity in different regions of the world. OBJECTIVE: The purpose of this cross-sectional study is to compare the severity of unilateral cleft lips in populations of Asia, sub-Saharan Africa, and Northern Africa and the Middle East. We hypothesize that the severity of unilateral cleft lips shows significant variation between populations. METHODS: Medical photographs of 780 patients with primary unilateral cleft lips treated by Operation Smile during November 2007 were reviewed. Photographs of 352 patients from Asia (China, Philippines, Vietnam, Laos, and Cambodia), 112 patients from the Middle East and North Africa (Jordan, Egypt and Morocco), and 316 patients from Sub-Saharan Africa (Ethiopia, Kenya and Madagascar) were analyzed. The severity of cleft lips was determined using the Fisher Method, which measures the columellar angle as a deviation of the columella from its normal vertical position. The angle was measured using a protractor with its base positioned along a line joining the lateral canthi. The angle between the protractor’s vertical axis and a line running through the columella was recorded. An analysis of variance (ANOVA) calculated statistical differences between each region and their respective countries. RESULTS: The Asian region was found to have the greatest severity of unilateral cleft lip deformity (p <.05). ANOVA tests show a significant difference between Asia and other regions studied. When stratifying the data by country, Philippines and Vietnam showed the highest severity. CONCLUSIONS: The results suggest a heterogenous pattern of global cleft lip severity. Unilateral cleft lips with highest severity were predominant in the Asian region. The observed phenotypical differences can be utilized in future studies of gene variability or environmental factors to determine the etiology of this significant disparity.

ARTHROSCOPIC FINDINGS IN ADHESIVE CAPSULITIS: THE HUMERAL HEAD GROOVE SIGN
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Background: Adhesive capsulitis or frozen shoulder describes the insidious onset of pain and progressive loss of active and passive range of motion in the glenohumeral joint. Adhesive capsulitis is a condition affecting middle age patients constituting at least 2% of the general population. It has long been considered a self-limiting disease, although complete resolution may take up to 2 years. For many patients this wait is not practical and they choose arthroscopic capsular release to alleviate their symptoms. The severity of the synovitis and adhesion of the long head of the biceps (LHB) tendon to the rotator interval have been found to negatively affect patient outcome scores. Capsulitis associated with contraction of the LHB tendon has been found to apply increased force on the humeral head and subsequently damage the corresponding areas of cartilage. To date, the extent of articular chondral damage seen in the “frozen shoulder” has not been quantified. Objective: We suggest severe adhesion combined with capsular contracture creates characteristic changes to the superior anterior portion of the humeral head corresponding to the path of the LHB tendon, and prolonged symptoms lead to more advanced chondral changes which are associated with decreased surgical outcome scores. Methods: Twenty-five patients who underwent arthroscopic capsular release were evaluated preoperatively and at end of healing. Patients were separated into non-grooved and grooved groups based on arthroscopic images taken during surgery and findings dictated in the operative report. Clinical assessment was translated into functional evaluation through the aid of the Constant Score (CS), Adjusted Constant Score (ACS) to allow appropriate comparison between patients, Simple Shoulder Test (SST), 10-point visual analog scale (VAS), and UCLA Score. Results: Non-grooved patients had statistically significant (p<0.05) better outcomes in four shoulder evaluation tools: CS, 81.6 to 64.6; ACS, 98.1 to 84.5; SST, 10.5 to 8.0; and UCLA, 32.6 to 28.2. Grooved patients presented with higher pain levels, 8.1 to 4.9 (p<0.01), and underwent longer physical therapy, 10 months to 6.2 (p=0.04) prior to surgery. Conclusion: Patients with very high pain complaints and prolonged preoperative physical therapy have an increased incidence of this previously unreported indentation of the humeral head. Patients with this finding had a less successful outcome after arthroscopic capsular release than those without.
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HYPOXIA INCREASES SUBSTANCE P/NK-1 RECEPTOR SIGNALING IN RAT MESOTHELIAL CELLS: AN EARLY EVENT IN PERITONEAL ADHESION FORMATION?
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Peritoneal adhesions are associated with serious post-operative complications, increased morbidity and mortality, and account for billions of dollars in health care expenditures. Studies in our laboratory have implicated Substance P (SP) in the formation of intraabdominal adhesions. Recent studies have demonstrated the ability of a neurokinin-1 receptor (NK-1R) antagonist to reduce peritoneal adhesions in a time and dose-dependent manner. The mechanism of action of the antagonist may be through modulation of the peritoneal fibrinolytic system, favoring degradation of the fibrin matrix. Tissue plasminogen activator (tPA), thought to be released by mesothelial cells lining the peritoneal cavity, is a key enzyme involved in peritoneal fibrinolytic activity and its release is inhibited by the action of SP. The objective of this project is to investigate the effect of surgically-induced hypoxia on the expression and activity of the NK-1R on primary cultures of rat mesothelial cells (RMCs). RMCs from rats undergoing laparotomy with the creation of ischemic buttons to induce adhesion formation were isolated and cultured, then exposed to either hypoxic (1% O2) or normoxic (21% O2) conditions for 24 hours. The cells were then incubated with SP at 10nM and 100nM, and subsequently assayed for MAP-Kinase activity by Western blot and tPA secretion into the media by ELISA. Tissues from ischemic buttons were also stained with a fluorescently labeled anti-NK-IR antibody to visualize receptors on the cell surface. We demonstrate that hypoxia over a period of 24 hours up-regulates the expression of NK-1R on the surface of RMCs and that these receptors activate SP-mediated cell signaling pathways, both of which are not seen under normoxic conditions. The up-regulation of NK-1R and increase in cell signaling may reduce the expression of tPA and thus influence the formation of peritoneal adhesions. These results indicate hypoxia may be a key player in the early events of peritoneal adhesion formation. Future studies include measuring mRNA transcript of tPA in hypoxic and normoxic cells and an assay with a hypoxia-inducible factor (HIF-1α) antagonist to ascertain the mechanism by which hypoxia up-regulates NK-1R expression.

Poster 40
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 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 electron transport chain 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) AKT ser473 phosphorylation, as well as GSK3 ser9 phosphorylation are reduced with Rotenone treatment, indicating again inactivation of the insulin signaling pathway; and (c) JNK, p38 MAPK, as well as their upstream kinases MKK4 and MKK3/6, bind to IRS-1 upon activation by Rotenone treatment, further suggesting that ROS-inactivation of insulin signaling involves JNK and p38 MAPK. We conclude that the insulin and the stress signaling pathways crosstalk and that the mitochondrial-generated ROS 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 41
MITOCHONDRIAL CALCIUM SIGNALING MEDIATES RHYTHMIC EXTRACELLULAR ATP ACCUMULATION IN SUPRACHIASMATIC NUCLEUS ASTROCYTES
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Cytosolic calcium is thought to be fundamental to the regulation of circadian systems. Rhythmic changes in cytosolic free Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(_{\text{c}}\)) have been observed in plant cells and mammalian SCN neurons. Intracellular free Ca\(^{2+}\) regulates cellular processes as diverse as membrane potential, enzymatic activity, gene expression, and transmitter release. Furthermore, both intracellular ATP content and extracellular ATP accumulation in the rat SCN are rhythmic. Since the expression of several genes involving ATP regulation and purinergic signaling are also rhythmic in the rat SCN and calcium signaling is a key regulator of mitochondrial ATP, we hypothesize that rhythmic cytoplasmic and mitochondrial calcium signaling pathways mediate clock-controlled rhythms in extracellular ATP accumulation in rat SCN cells. We recently demonstrated that ATP accumulates in the culture medium of an immortalized rat SCN2.2 cell line in vitro. Thus, we have utilized this SCN culture system to test the idea that calcium signaling, particularly in SCN2.2 astrocytes, is mechanistically linked to rhythmic extracellular accumulation of ATP. Astrocytes communicate via the release and reception of ATP and they express purinergic receptors implicated in calcium signaling and gliotransmission. Furthermore, astrocytes display circadian rhythms in the expression of mammalian clock genes and glia-specific genes that are required for circadian locomotor behavior in Drosophila. Still, the importance of these molecular rhythms in glial function is unknown. Here, we demonstrate that rhythms of extracellular ATP accumulation in SCN2.2 cell cultures coincide with rhythmic elevations in mitochondrial calcium and that disruption of mitochondria calcium transport abolishes the ATP accumulation rhythm. Also, since calcium signaling has been implicated in apoptosis and cell division processes, we demonstrate that these rhythms of extracellular ATP accumulation are not a by-product of rhythmic cell cycle or rhythmic cell death and are a likely output of the biological clock. Future research will be important to determine the role of clock-controlled ATP signaling in astrocytes in the mammalian brain, perhaps in the regulation of brain metabolism, the regulation of sleep/wake physiology, or the integration of both.

Poster 42
INTERRELATIONSHIP BETWEEN OXIDATIVE STRESS, MITOCHONDRIAL DYSFUNCTION AND CELL DEATH IN HCV INFECTION
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Increased reactive oxygen species (ROS) production is a prominent feature of chronic Hepatitis C infection and appears to be a calcium dependent phenomenon caused by viral protein interactions at the ER-mitochondrial axis. Recently it has been observed that HCV infection in cell culture has cytopathic effects that are associated with mitochondrial depolarization and permeability transition, but whether these events are related and whether ROS production is a key trigger of viral-induced apoptosis is unknown. The AIM of this study was to determine the time course of ROS production, mitochondrial depolarization and apoptosis in viral infection and determine whether an ROS burst was required for cell death. METHODS: Human Hepatoma (Huh7) cells infected with the JFH1 strain of HCV and genome-length replicons were used. ROS production was assayed using Amplex Red assay. Mitochondrial depolarization was measured by JC-1 flow cytometry and cell death was determined by AnnexinV/7AAD staining. RESULTS: Infection of Huh7 cells with JFH1 resulted in a progressive increase in H2O2 production that peaked at 7 days. This coincided with high levels of virus production and phosphorylation of JNK and p38 MAP kinases and was correlated with high levels of apoptosis as evidenced by PARP cleavage, caspase 3 activation and AnnexinV binding. To determine if ROS production contributed to cell death, we studied infected Huh7 cells at day 3 after infection, a time at which viral replication is present, MAPK activation has occurred, and spontaneous ROS production, even though present, has not peaked. At this time there was minimal cell death (5-10%). Addition of 0.2 mM tBOOH for 4 hours, a treatment that had no effect on uninfected cells, induced mitochondrial depolarization and massive apoptosis (30-40%) in infected cells. To determine if greater ROS production was the trigger for mitochondrial depolarization and cell death in infected cells we studied genome-length HCV replicon bearing Huh7 cells. Similarly to infected cells, these cells displayed marked sensitivity to tBOOH induced mitochondrial depolarization and cell death. tBOOH-induced mitochondrial depolarization was completely inhibited by preincubation of the cells with a cell permeant astaxanthin derivative that blocked spontaneous ROS production. CONCLUSION: HCV infection caused mitochondrial sensitization to ROS but was not sufficient to initiate the cell death program without additional ROS accumulation.
**Poster 43**  
**ASSESSMENT OF AH RECEPTOR ACTIVITY IN THE ABSENCE OF AN EXOGENOUS LIGAND**  
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The aryl hydrocarbon receptor (AhR) is traditionally recognized for its role in the adaptive metabolism of xenobiotics, but has more recently been associated with important physiological processes such as cell cycle regulation and apoptosis. Our lab has recently followed up on observations suggesting that the AhR is able to promote cell survival or death in response to intrinsic or extrinsic apoptotic stimuli, respectively. Using primary hepatocytes isolated from the AhR<sup>fx/fx</sup> mouse, we generated AhR null hepatocytes through infection with an adenovirus expressing the Cre recombinase. Complete loss of AhR expression occurred within 24 hours. AhR expression was unaltered in control cultures infected with a control adenovirus. Susceptibility to UV-irradiation induced apoptosis was assayed by measuring caspase-3 activity, and monitoring chromatin condensation and cell blebbing. Since Akt activity was recently implicated in promoting AhR-mediated Hepa-1 cell survival upon intrinsic stimulation, we examined Akt expression and activity in the primary hepatocytes immunologically. Our findings confirmed that the AhR indeed promotes survival, but does so involving a mechanism independent of Akt activity. In order to ascertain how the AhR functions to protect primary hepatocytes from intrinsic cell death, we performed a detailed DNA microarray analysis linking changes in the transcriptome directly to the loss of AhR expression—in the absence of an exogenous receptor agonist. This screen represents a unique strategy for assessing the receptor’s physiological role in regulating gene expression, and identified a distinct set of genes with altered expression not previously associated with AhR function. As a result, we are now in position to characterize new AhR-dependent target genes and mechanisms, including protection from apoptosis, consistent with normal AhR physiology.

**Poster 44**  
**RESTRAINT OF BMP SIGNALING BY PPM1H, A NOVEL PHOSPHATASE TOWARDS SMAD DEPHOSPHORYLATION IN THE CYTOPLASMA**  
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Bone Morphogenetic Proteins (BMPs) belong to the TGF-beta superfamily that regulates a wide array of cell functions and behaviors. The key step of BMP signal transduction is the BMP receptor-mediated phosphorylation of transcription factor Smad1, 5 and 8 (collectively Smad1/5/8), which leads to the activation of BMP-induced gene transcription in the nucleus. In this study, we described the identification and characterization of PPM1H, a novel cytoplasm-localized Smad1/5/8-specific phosphatase. By using a series of biochemical and cellular assays, we found that PPM1H directly interacts with Smad1 in the cytoplasm, and dephosphorylates phospho-Smad1/5/8 (P-Smad1/5/8). Ectopic expression of PPM1H abolished BMP-induced gene expression, and conversely, loss of PPM1H activity or expression greatly enhanced BMP signaling. In conclusion, this study suggests that PPM1H acts as a gatekeeper to prevent excessive BMP signaling through dephosphorylation and subsequent nuclear exclusion of Smad proteins.
Glycoproteins result from the most common type of post-translational modification (glycosylation) and play an important role in various cellular processes that are thought to be altered with aging, including the regulation of cell-to-cell and cell-to-matrix interactions. Certain glycoproteins have been shown to be altered in aging, such as IGF-1 and IL-6; however, to our knowledge no study has performed a comprehensive analysis of the plasma glycoproteome with age or frailty, a geriatric syndrome which contributes to functional decline. To compare the plasma glycoproteome by age (young vs. non-frail older) and frailty (non-frail vs. frail), subjects included 4 non-frail and 4 nonfrail community-dwelling older adults and 4 healthy young adults, who were sex-matched and age-matched (for frail comparison only). Frailty was defined as the presence of three of five characteristics: slow walking, weakness, exhaustion, weight loss, and low physical activity. Plasma was applied to Concanavalin A (ConA) lectin columns. After incubation, 2-dimensional polyacrylamide gel electrophoresis was performed on the eluate, and at least 200 glycoproteins were separated and resolved. Gel images were quantified using PDQuest software (Bio-Rad, Inc.), and glycoproteins with a 2-fold or greater difference between comparison groups (young vs. older or non-frail vs. frail) were subsequently identified by matrix-assisted laser desorption/ionization time of flight spectrometry. Our analyses showed that antithrombin III variant, immunoglobulin light chain, and α-2-macroglobulin were up-regulated in older adults compared to young adults, and that Complement Component (C-terminus) was down-regulated in non-frail compared to frail older adults. This research shows several glycoproteins to differ with aging and one glycoprotein to differ with frailty. These glycoproteins, related to inflammation and the hematologic system are not unexpected, but may not have been hypothesized without this high throughput discovery technique. Further, using these methods to better understand the physiologic basis of aging and frailty, may lead to biomarkers of frailty and potential future interventions for this devastating syndrome.
NEURONAL DELETION OF FTO, THE ORTHOLOG OF AN HUMAN OBESITY-ASSOCIATED GENE, RESULTS IN GROWTH RETARDATION IN MICE
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Fto (fat mass and obesity associated) has been identified as an obesity-susceptibility gene by several independent large scale genome association studies. A cluster of SNPs (single nucleotide polymorphism) located in the first intron of FTO has been found to correlate with obesity-related traits, such as body mass index, hip circumference, and body weight. This association has been observed in both children and adults, as well as in populations of various ethnicities. The protein encoded by Fto is highly conserved among vertebrates, and has been predicted to be a member of the non-heme and 2-oxoglutarate-dependent dioxygenase superfamily. However, the physiological function of FTO is not fully understood. We generated Fto knockout mice using the Cre-loxP system. A conditional knockout line (FtoF/F) was first constructed by flanking exon3, the largest exon in Fto, with two loxP sites. It was then crossed to Meox2-cre to achieve whole body knockout. Homozygous knockout mice (Fto Δ/Δ) are viable, and the absence of Fto protein was confirmed by Western blot. Deletion of Fto in mice results in postnatal growth retardation immediately after birth, but doesn't affect embryo development. The knockout mice are just 60% the weight of wild-type littermates at the time of weaning. The runted phenotype of Fto Δ/Δ mice persists into adulthood with shorter body length and reduced bone mineral density. Fto Δ/Δ mice also have reduced serum level of IGF-1 during adolescence comparing to wild-type littermates. The body composition (fat/tissue %) of adult Fto Δ/Δ mice is similar to that of wildtype and herterozygotes littermates, suggesting that Fto does not function directly in fat tissues. Brain-specific Fto knockout mice (Fto NΔ) were generated by crossing FtoF/F mice with Nestin-Cre. Deletion of Fto in the brain leads to similar phenotypes as that of whole body knockout. The Fto NΔ mice have smaller body weight, shorter body length and reduced bone mineral density as compared to the control (FtoF/F). They also have reduced serum level of IGF-1 during adolescence. This suggests that Fto functions in the brain, most likely in the neuroendocrine system, to regulate systematic growth.

IN VIVO FUNCTIONAL ANALYSIS OF ENGRAILED2 (EN2) ASD ASSOCIATED HAPLOTYPE
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Autism Spectrum Disorders (ASD) is a complex neuropsychiatric disorder with a strong genetic basis. EN2 - a homeobox transcription factor - has been one of the candidate genes associated with ASD. Previous work done in our lab strongly indicates the two intronic SNPs of EN2 as ASD risk alleles. The major alleles A of rs1861972 and C of rs1861973 were observed to be significantly over transmitted to off springs affected with ASD, while the minor alleles G and T respectively were under transmitted. The over transmission of the major alleles was more significant as a haplotype (P-value < .000001). In vitro functional studies such as Luciferase assays demonstrate increased gene expression with the A-C haplotype (A-C) as compared to the G-T haplotype (G-T). Electro Mobility Shift Assays also demonstrate differential binding of nuclear proteins to the A and C alleles. The above data demonstrates that A-C, an ASD risk allele, is functional in vitro. After observing the above results, the next important step is to test for A-C function in vivo. EN2 has a dynamic expression pattern throughout CNS development, which leads us to ask if the A-C haplotype is functional at more than one developmental time points in more than one cell type, and if the haplotype always increases gene expression during CNS development?To investigate the in vivo functional role of rs1861972-rs1861973 during CNS development, transgenic mouse lines were generated for the autism associated A-C haplotype (A-C) and the other common G-T haplotype (G-T). Each transgene contains ~25 kb of EN2 cis-regulatory sequence and a fluorescent reporter to detect spatio-temporal expression differences. 6 lines for A-C and 8 lines for G-T with varying copy numbers were successfully established. Reporter fluorescence was observed in all lines similar to that of endogenous EN2 in adults. All the lines were analyzed for spatio-temporal and level expression of the transgene. Histological analyses done on postnatal and adult stages suggest a similar spatial expression pattern between the two haplotypes. RT-qPCR analyses done to measure expression level differences between the two haplotypes, revealed that A-C is functional in vivo and it increases gene expression in postnatal (96% increase, P-value<0.0001) and adult stages (200% increase, P-value<0.00001). Similar analyses to be done in the embryonic stages will help determine when, where and how the ASD-associated A-C haplotype functions during development.
**Poster 49**

**MOLECULAR AND HISTOPATHOLOGICAL CHANGES IN MOUSE INTESTINAL TISSUE AFTER PROTON EXPOSURE**

Ye Zhang and Honglu Wu  
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Radiation in space, especially energetic protons emitted from solar particle events (SPE’s), poses serious health risks to astronauts and is especially dangerous for long duration missions. Protons are the most abundant particles in space and to date there is little known about the details of the negative consequences crew members will face upon exposure to them. To elucidate some of the possible health effects induced by protons, BALB/C mice were subjected to 250 MeV of proton radiation at doses of 0 Gy, 0.1 Gy, 1 Gy, and 2 Gy. Three specimens per dose were studied. The gastrointestinal tract of each animal was dissected four hours post-irradiation and the isolated small intestinal tissue was fixed in formalin for histopathological examination or snap-frozen in liquid nitrogen for RNA isolation. Histopathologic observation of the tissue using standard H&E staining methods to screen for morphologic changes showed a marked increase in apoptotic lesions for even the lowest dose of 0.1 Gy, and the dose response showed a possible higher sensitivity at low dose. Tissue of the gastrointestinal tract was also homogenized and RNA was isolated for cDNA synthesis and real-time PCR analysis for genes involved in apoptosis. Results of gene expression changes revealed consistent up or down regulation of a number of genes for all of the exposure doses, including Cd40 and Hsp90ab1, that may play a role in proton-induced apoptosis. In addition, several genes were found to have significant changes in the RNA level after only the low dose (0.1 Gy), but not the high dose (1 and 2 Gy), proton exposures (e.g. Bok and Casp1), whereas some genes had expression changes only after high dose proton exposures (e.g. Tsc22d3). These findings demonstrated that apoptosis may occur in gastrointestinal tracts after even low dose proton exposures, and the different gene expression patterns between low and high dose proton irradiated mice may offer insight into the molecular mechanisms of the possible high sensitivity at low proton doses.

**Poster 50**

**AGE-SPECIFIC NATURAL GENETIC VARIATION INFLUENCING QUANTITATIVE TRAITS IN DROSOPHILA MELANOGASTER**

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Senescence is the age related decline in physiological performance. When senescence is observed in an organism, it is debatable if there is a general decline in function across all traits or if certain traits decline at varied rates. Along with understanding the complexity of senescence, addressing how this variation is maintained across quantitative traits and the potential interrelationships among traits has also been quite ambiguous. The interrelationships among traits are largely due to how energy is allocated in the aging organism. Energy expended for one trait has an impact on the availability energy for other traits and so causes physiological trade-offs that directly affect the development, growth, reproduction, maintenance, and survival of an organism. Understanding the effect of age on allocation patterns among traits and the inheritance of these allocation patterns will greatly contribute to our understanding of senescence. This study investigates the genetic basis of naturally occurring variation in quantitative traits while addressing the influence of senescence on quantitative traits in Drosophila melanogaster. Naturally occurring genetic variation was identified by using a panel of chromosome substitution lines derived from a natural population in Raleigh, NC. Next, phenotypic variation was observed in four quantitative traits: immune response, reproduction, energy storage, and lifespan. These observations documented the variation in survival and fitness traits and elucidated physiological trade-offs associated with energy distribution. Lastly, the influence of senescence on each of the previously mentioned traits (except lifespan) at two ages (1 week and 6 weeks of age) to identify age related changes for each trait. Results from this study have examined: (1) the relative amount of age-specific genetic variation for each trait and the degree of genetic correlation for each trait at each age, (2) genetically based age related differences within each trait, (3) age-specific genetic correlations and estimates of genetic variance components for each trait. Future directions would be to identify the genes that are responsible for the variation observed in this study through quantitative trait loci mapping or genome wide association studies.
CHARACTERIZATION OF LYMPHOCYTIC CHORIOMENINGITIS VIRUS INFECTION OF HUMAN PLACENTA
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Background: Lymphocytic choriomeningitis virus (LCMV) is a prototypical arenavirus that usually causes asymptomatic illness in the immunocompetent patient. However, there has been a recent rise in reported cases of congenital LCMV intrauterine infection, with associated adverse outcome of pregnancy. Inflammatory cytokines, such as interferon (IFN)-γ, interleukin (IL)-6, and tumor necrosis factor (TNF)-α have been linked to adverse pregnancy outcomes. However, the relationship between productive viral infection and these placental inflammatory mediators remains unknown. We used LCMV as a model to study the innate immune response to viral infection in the placenta and its relationship with viral replication. Methods: First trimester trophoblast cell line HTR8-SV40Neo (HTR) was cultured using standard methods. Placentas were obtained from term deliveries and samples of placental villi excised. Inoculation was performed with LCMV Armstrong strain. Plaque assays were used to assess replication of virus in HTR cells and term explants. Immunoassay was used to detect TNF-α, IFN-α, IFN-γ, and IL-6 secretion in term explants, with confirmation by quantitative real-time reverse transcriptase polymerase chain reaction (RT-PCR). Results: LCMV exhibited replication in HTR cells, but did not replicate in term explants. Secretion of TNF-α was found in term placental explants infected with LCMV (p = 0.53), which was confirmed using RT-PCR. Placental explant also demonstrated induction of IL-6 and IFN-α by RT-PCR, but an effect on IFN-γ was not found. These data suggest that while LCMV may be capable of productive infection in first-trimester placenta, term placental villi are unable to support LCMV replication. However, abortive viral infection may still induce an inflammatory response from the placenta. Conclusions: The innate immune response to LCMV infection of term placental explants may prevent productive viral replication via a type I IFN pathway. Further experiments will determine whether replication of LCMV in HTR cells induces a similar IFN response. LCMV NS3 protein is known to block IFN-stimulated gene transcription in other systems, and LCMV replication is also known to be inhibited by IFN. The absence of IFN-γ production in response to viral infection of term placenta suggests further studies to characterize the maternal innate immune system in light of the increased susceptibility of the mother and fetus to viral infections.

INITIATION OF ADIPOSE TISSUE INFLAMMATION FOLLOWING HIGH SATURATED FAT DIET
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Obesity has become a major health risk in most developed countries. Recent studies in humans and animal models have shown adipose tissue (AT) to exhibit an inflammatory response to obesigenic diets that is characterized by infiltration of leukocytes and expression of inflammatory cytokines and chemokines. This response appears to contribute critically to the systemic inflammatory complications of obesity. Since most of the data comes from AT collected after obesity is established, there is little information available on the early changes as a result of high saturated fat (HSF) diet. In vitro a variety of cell types are activated by treatment with saturated fatty-acids and this response is mediated through TLR4 and TLR2. A single HSF meal induces transient endotoxemia and leukocyte activation in both the mouse and human, while three days of HSF diet results in neutrophil infiltration and expression changes of inflammatory genes in the murine intra-abdominal AT. The possible roles and interaction of leukocytes resident in AT, in circulation and the AT-surrounded lymphatics following HSF feeding are unclear. The goal of this project is to analyze the very early local and systemic response to HSF feeding and the cells which initiate this response. I hypothesize that leukocytes resident in the AT initiate early changes and TLRs are necessary for their activation. To test this hypothesis we have examined molecular and cellular changes in the blood and intra-abdominal AT which contain or do not contain lymph nodes, in a murine model of HSF feeding and utilize the TLR4 deficient, TLR2/-/- and leukocyte depleted mouse models. Completed experiments show that three days of HSF feeding of wildtype mice caused significant increases in CCL2, F4/80 and CXCL1 expression in the intra-abdominal AT containing lymph nodes, but no changes were seen in AT without lymph nodes. In TLR2/-/- mice, CCL2 expression increased, but not F4/80, indicating that TLR2 may not be involved in chemokine expression but is necessary for macrophage infiltration. A trend towards increased inflammatory gene expression (IL-1β, TNF, F4/80) in the blood suggests that this response is systemic.
Among the top infectious disease killers, methicillin-resistant Staphylococcus aureus (MRSA) possesses the ability to survive a multitude of harsh conditions encountered during the infection process. MRSA has demonstrated shear-dependent regulation of virulence factors in the high fluid shear environment of the blood. As an intestinal colonizer, MRSA experiences the low fluid shear conditions descriptive of components of this host site. While the outcome of low fluid shear culture has been investigated for several bacterial pathogens, little has been done to understand how this environmental factor affects MRSA. We hypothesize that MRSA will exhibit an evolutionarily conserved response mechanism to low-shear conditions, and this environment will impart modifications to the virulence of the organism. NASA developed rotating wall vessels were used to achieve a low fluid shear culture environment. Culture of MRSA in the low-shear condition resulted in lower cell concentrations as well as a reduction in carotenoid production, pigments responsible for their yellow/gold coloration. When exposed to various environmental stressors, post low-shear culture, a decrease in the ability to survive oxidative assault was observed. The low fluid shear environment also resulted in a decrease in hemolysin secretion, a staphylococcal toxin responsible for red blood cell lysis. When challenged by the immune components present in human whole blood, low-shear cultured MRSA demonstrated significantly reduced survival rates. Assays to determine the duration of these alterations demonstrated that the low-shear response could be lost in as few as 2.5 hours. Microarray analysis of low-shear cultured MRSA revealed the differential regulation of genes involved in metabolism, stress response, and phosphate transfer. Additional genetic analysis with quantitative real-time PCR revealed alterations in the expression of Hfq, the conserved RNA chaperone protein involved in global gene regulation which has been connected to the regulation of a low-shear response in Gram negative pathogens. These findings in MRSA suggest an evolutionary conserved response to low fluid shear conditions among structurally-diverse microorganisms. Furthermore, the reduction in pigmentation, hemolysin secretion, and survival against oxidative stress and immunologically active whole blood demonstrate an overall decrease in the virulence factors of MRSA in response to a low fluid shear environment.

**Poster 54**

**EVALUATION OF ANTIRETROVIRAL TREATMENT OUTCOMES AMONG HIV-INFECTED CHILDREN IN A COMPREHENSIVE CARE CLINIC IN LA ROMANA, DOMINICAN REPUBLIC**

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**BACKGROUND:** Relatively few studies have examined the response to antiretroviral therapy (ART) among children in resource-limited settings (RLS). In the Dominican Republic (DR), a middle-income country with a generalized HIV epidemic, every treatment failure necessitates a switch to a second-line regimen that is more costly and difficult to procure. **OBJECTIVE:** To identify predictors of treatment failure among children receiving ART at the Clínica de Familia MIR (CFMIR), a comprehensive care clinic and HIV referral center in the southeastern DR. **METHODS:** This is a retrospective study of children on ART at CFMIR from October 2004 to December 2009. Sociodemographic and clinical data were extracted from charts of children on ART. In the absence of plasma HIV RNA concentration monitoring, treatment failure was defined as initiation of second-line ART. **RESULTS:** Of 110 children who received at least 12 mos of ART, 80 medical records were reviewed at random. The starting ART regimen was NNRTI-based for 69 (86.2%) patients and PI-based for 11 (13.8%). Six (7.5%) patients died; the median time on treatment before death was 26 days (interquartile range [IQR] 17-288 days). Fourteen (17.5%) patients experienced treatment failure and initiated second-line ART. Of these 14 who failed first-line ART, the median age at initiation of ART was 7 yrs (IQR 4-11 yrs), 7 (54%) were orphaned, and 2 (15%) resided in bateys (sugarcane plantation settlements of primarily Haitian migrants and their families). Median duration of first-line ART before regimen switch was 21 mos (IQR 18-27 mos). Median CD4% at initiation of first- and second-line ART were 11.2% (IQR 6.4-11.4%) and 13.4% (IQR 9.1-17.0%), respectively. Patients who failed first-line ART had a lower median CD4% at ART initiation than those who did not (11.2% versus 21.6%, p=0.005), and more severe clinical presentation as defined by CDC stage C (100% versus 73.3%, p=0.056). No association was observed between treatment failure and baseline anemia or malnutrition. **CONCLUSIONS:** Treatment failure was associated with clinical and immunological disease severity at initiation of ART. Prompt diagnosis of HIV and early treatment are critical actions to reduce the risk of subsequent treatment failure. Further analysis to identify additional predictors of treatment failure will enhance CFMIR's ability to target high-risk children for early intervention and inform treatment initiatives elsewhere in the DR and in other RLS.
High Mobility Group Box 1 (HMGB1) functions in the nucleus as a DNA binding protein that increases stability for transcription factor interactions. HMGB1 is a late mediator of inflammation and functions as a danger signal when released from damaged tissues. HMGB1 expression is up-regulated in sera and tissues of patients with rheumatoid arthritis, sepsis, multiple sclerosis, ischemia, and many other inflammatory conditions. Blocking antibodies to HMGB1 reduce inflammation in animal models of sepsis and rheumatoid arthritis, yet the mechanism of HMGB1 mediated inflammation is unclear. HMGB1-/- mice die early, thus we have developed transgenic mouse models to over-express HMGB1 in a cell specific manner. IRES-EGFP has been engineered into expression constructs so that HMGB1 expression can be followed with GFP. Over-expression of HMGB1 does not show altered immune cell maintenance nor are there significant differences in development of B and T cell populations. Collagen induced arthritis (CIA), the mouse model of rheumatoid arthritis and experimental autoimmune encephalomyelitis (EAE), the mouse model of multiple sclerosis have been induced to test the function of HMGB1 over-expression in-vivo. Transgenic mice have increased clinical scores and inflammatory responses at antigen specific restimulation. These studies more clearly define HMGB1 as a proinflammatory mediator in inflammation.

The recent outbreaks of H5N1 avian and H1N1 swine-origin influenza underscore the need for a universal vaccine strategy that will protect against both seasonal and pandemic strains of the influenza A virus. We hypothesize that this strategy will need to elicit both systemic and mucosal antibody and T cell immune responses targeting antigens that are highly conserved among all strains of the virus. The ectodomain of the Matrix Protein 2 (M2e) is highly conserved in all strains and thus represents an attractive vaccine target. However, it is poorly immunogenic in individuals during flu infection, and current licensed vaccines cannot elicit strong antibody responses against this antigen. To improve the immunogenicity of M2e, we developed a Particle Mediated Epidermal Delivered (PMED) DNA vaccine that expresses the M2e gene as a fusion with a highly immunogenic Hepatitis B core carrier antigen (HBc) (M2e-HBc DNA vaccine). The objectives of our initial proof-of-concept study were to: 1) Evaluate whether the HBc carrier improved the immunogenicity of M2e in our DNA vaccine and 2) Evaluate whether the PMED delivery of M2e-HBc DNA vaccine elicits more robust M2e-specific immune responses in mice compared to a experimental M2e-vaccine currently in clinical trials (M2e-HBc protein vaccine). Systemic and mucosal M2e-specific antibody and T-cell responses were measured in mice following vaccination with M2 (full length M2e gene) DNA alone, M2e-HBc DNA, or M2e-HBc recombinant protein. The M2e -HBc DNA vaccine was found to induce significantly higher magnitude M2e -specific antibody and T cell responses in mice when compared to vaccination with the full length M2 DNA alone or the M2e-HBc protein vaccine. Our results demonstrate the feasibility of the M2e-HBc DNA vaccine approach as a strategy to induce strong immune responses against this highly conserved antigen. These results support further investigation into this approach as a potential universal vaccine strategy for protection against both seasonal and pandemic influenza A viruses.
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ROLE OF γδ T CELLS IN MURINE DIETARY OBESITY
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Obesity often results in a state of chronic low-grade systemic inflammation. Studies have shown that there is an infiltration of lymphocytes and macrophages, and an increase in pro-inflammatory cytokines in the adipose tissue in diet-induced obesity in mice. T cell numbers in the epididymal fat pad of C57BL6 mice, fed a diet high in saturated fatty acids ("Western" diet, 21% by weight milk fat) for five to ten weeks, have been found to be greater than that in mice on regular chow. γδ T cells make up about one-third of this T cell population in the epididymal adipose tissue in the normal as well as obese state, and apparently play an important role in inflammatory response in adipose tissue. We have shown that TCRδ/-/ mice lacking γδ T cells failed to recruit macrophages into adipose tissues or increase expression of cytokines such as MCP-1, IL-6, IFN-γ, IL-10. In additional studies, γδ T cells were depleted in wildtype mice by i.p. administering anti-TCRδ antibody. A decrease in macrophage marker F4/80 and IL-10 was observed in these mice on the high fat diet (HFD) as compared to saline-treated control mice on HFD. IFN-γ mRNA levels were also found to be elevated in HFD-fed mice. When γδ T cells were depleted from the lymphocyte fraction of the epididymal fat pad of stromal vascular fraction, IFN-γ level significantly decreased, suggesting the γδ T cells are producers of IFN-γ in obese mice. This was supported by flow cytometry where a fraction of γδ T cells present in the stromal vascular fraction obtained by collagenase digestion of the fat pad were CD122+, a marker for IFN-γ-producing γδ T cells in the periphery. A number of subsets of γδ T cells exist but little is known about which ones play a role in regulating inflammation in adipose tissue. The γδ T cell subsets observed in epididymal adipose tissue of WT mice were found to be Vγ2,4,5,6 and Vδ3,4 which were also present in mice on HFD for 5 weeks. In contrast to the reduced inflammatory response, adiposity of TCRδ/-/ mice on HFD was equal to that of wildtype mice. Analysis of adipose tissue, though, revealed smaller adipocytes in the TCRδ/-/ with a greater number/unit area. Thus, it appears that the γδ T cell knockout mice in an obese state have markedly reduced inflammation compared to obese wild type mice. This may permit more efficient differentiation of preadipocytes to adipocytes in response to increased dietary lipid.

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INVESTIGATION OF TLR LIGAND-GENERATED INFLAMMATORY SIGNALS FOR THE INDUCTION OF HIGH MAGNITUDE MEMORY CD8+ T LYMPHOCYTE RESPONSES
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Background: Most currently used vaccines elicit antibody and CD4+ T lymphocytes, but protection against some pathogens may also require a CD8+ T cell response. CpG ODN, Poly(I:C) and MPL adjuvants greatly enhance the magnitude and longevity of immune responses during vaccination due to its ability to stimulate TLRs. Bone marrow-derived dendritic cells (BMDC) alone are shown to induce protective T cell responses against fatal HSV-2 infection. Objective: To enhance the ability of these effective methods for further vaccine potential, we plan to combine the CD8+ T cell stimulating BMDC with adjuvants that will generate a more potent interaction between them. We believe that different TLR ligands will differentially shape the antigen-specific CD8+ T cell memory response, in turn, providing greater protection from subsequent infection. Retention of those cells at sites pertinent to infection may vary depending on the third signals provided by antigen presenting cells present at the time of CD8+ T cell activation. We chose these particular TLR agonists because TLR4 (MPL) and TLR9 (CpG) ligands elicit high IL-12 and low IFN-α/β, while TLR3 (Poly(I:C)) ligands generate the opposite cytokine response. Methods: We examined the ability of specific TLR agonists to stimulate a specific third signal in BMDC necessary for appropriate development of antigen-specific memory CD8+ T cells against HSV-2. This was done by stimulating mature BMDC in vitro, pulsing them with HSV-2 antigen and then co-culturing them with HSV-2-specific CD8+ T cells. Flow cytometry was used to examine the in vitro-cultured CD8+ T cell characteristics. Results: Initial in vitro studies demonstrated that gB peptide-specific CD8+ T cells co-cultured with gB-pulsed, TLR ligand-treated BMDC had a more activated phenotype, but there was little difference in CD8+ T cell proliferation when compared to media-treated BMDC cultures. Upon restimulation, the activated CD8+ T cells produced high quantities of TNF-α, IFN-γ, and granzyme B, but variation between groups was minor. Conclusions: These results suggest the choice of TLR ligand for stimulation had little impact on CD8+ T cells in vitro. Further experiments will focus on examining the lymphoid tissues to which our CD8+ T cells reside, their activation status, cytokine production profiles, and cell surface chemokine receptor expression directed by in vivo delivery of antigen-pulsed, TLR ligand-treated BMDC.
INTERFERON-GAMMA WITH INTERFERON ALPHA AND RIBAVIRIN FOR HEPATITIS C NON-RESPONDERS
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Background: When administered simultaneously, interferon-alpha 2b + interferon-gamma result in dramatic antiviral synergy. Ribavirin has shown to enhance interferon-gamma levels in patients with chronic hepatitis C treated with interferon-alpha. Enhancement of immune responses, especially those related to type-1 T helper cell activity, may contribute to better efficacy in combining ribavirin with IFN-alpha for treatment of chronic hepatitis C.

Objective: The aim of the present study was to evaluate the efficacy and safety of triple combination regimens comprising of interferon alfa-2b and ribavirin plus either interferon gamma or amantadine in HCV genotype 3 infected patients who have not previously responded to interferon alpha (standard or pegylated) in combination of ribavirin.

Methods: Patients were randomized to receive interferon alpha 2b 3MU t.i.w, ribavirin 800-1200 mg per day with either interferon gamma 2 MU t.i.w or amantadine 100 mg twice daily. Treatment was continued for 48 weeks in patients showing complete or partial (2 log reduction) early virological response (EVR) at 12 weeks and negative PCR at 24 weeks.

Results: Total enrollments were 44. Mean age 44.1 years (28-60); 25 were previously non-responders out of them 12 were in the gamma arm. Nineteen were relapsers, out of them 10 received Gamma interferon. F3 or F4 fibrosis was seen in 14 (34%) and 9 (23%) were diabetic. By intention-to-treat analysis, the EVR for interferon gamma arm was 50% (11 out of 22) and for amantadine arm 36.36% (8 out of 22) (p = 0.272).

The end of treatment responses were 45% (10/22) & 27% (6/22) for interferon gamma and amantadine arms respectively (p= 0.174). Overall sustained virological response (SVR) with triple regimens was seen in 34% (15/44), SVR was 45% (10/22) in the gamma arm and 23% (5/22) in the amantadine arm. In the subgroup analysis, this figure was 60% (6/10) and 44% (4/9) for relapers, and 33% (4/12) and 8% (1/13) for non-responders in both arms respectively. Treatment was well tolerated in both arms. Conclusions: About one third of genotype 3 patients who had not previously responded well to the interferon and ribavirin responded to the triple regimens. However addition of interferon gamma was a better option with an acceptable safety profile. Its combination with pegylated interferon and ribavirin needs further evaluation in a larger clinical trial.

STIMULANT USE INCREASES SUSCEPTIBILITY TO HSV-2 IN MURINE MODELS OF GENITAL HERPES
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Background: In 2006, 24.7 million individuals aged 15-64 used amphetamine type stimulants including methamphetamine (METH) and 3,4-Methylenedioxymethamphetamine (MDMA). There is a known association between stimulant use and an increased incidence of HIV and other sexually transmitted infections (STI). Although behavioral disinhibition is important in this association, there is increasing evidence that other biological factors contribute.

Objective: To examine the impact of stimulant use on infection with an important STI pathogen, Herpes Simplex Virus type 2 (HSV-2) in established murine models of genital herpes.

Methods: Female or male inbred mice were treated for 5 days with METH, MDMA, or saline via subcutaneous injection. Animals were intravaginally or intrarectally challenged with HSV-2 on the 3rd day of treatment. Vaginal swab samples were collected to determine viral replication. All mice were examined daily to day 21 post infection for clinical signs of genital herpes. Dorsal root ganglia and spinal cord DNA samples were analyzed by quantitative PCR. Cytometric bead arrays were used to quantify a panel of cytokines in animal tissue and systemic samples.

Results: In these studies we show that both MDMA and METH dysregulate systemic and mucosal innate immune responses to vaginal HSV-2 challenge. These effects are associated with significantly altered susceptibility to disease. In similar studies using a rectal virus challenge, METH use produced gender-specific differences in disease. Female treated mice experienced significantly earlier disease onset compared to controls, but no difference was seen in male animals. Conclusions: Our observations have important public health implications in understanding the relationship between stimulant abuse and STI risk that may in effect contribute to controlling the spread of genital herpes and other STIs. Further studies will investigate the immune mechanisms behind increased susceptibility to HSV-2 attributed to stimulant abuse.
Children with Attention Deficit Hyperactivity Disorder (ADHD) lag behind their peers in motor development, showing persistence of neurological signs such as motor overflow and dysrhythmia. This has been demonstrated in case control studies using a developmental assessment tool called the Physical and Neurological Assessment of Neurological Subtle Signs (PANESS). Another important feature of typical motor and cognitive maturation in childhood is increased speed and decreased variability of reaction times. We hypothesized therefore that both PANESS scores and reaction time parameters would not mature normally in ADHD vs. typical children and moreover that these abnormalities would be correlated. We evaluated both in 21 children with ADHD and 16 typical controls, ages 8 to 14 years. Compared to typical children, in ADHD children both simple and choice reaction times were significantly slower and variability significantly higher, and improvement with age was less. PANESS scores were significantly higher in ADHD children and these correlated with both slower reaction times and greater reaction time variability. We conclude that both PANESS and reaction times reflect neurodevelopmental delays which may have similar neurobiological mechanisms. Each functions as an objective marker of the presence of the behavioral diagnosis of ADHD in children aged 8-14 years.

Alzheimer's disease (AD) is a neurodegenerative disorder associated with multisystem cognitive deficits and functional impairment. AD affects an estimated 26.6 million people worldwide and accounts for 50-70 percent of all dementia. MRI studies have shown marked cerebral atrophy in patients with late stage AD, due to neuronal cell death. Neurogenesis has been thought to end early in development; however, it continues to occur in the dentate gyrus (DG) in adult neurons. Understanding the mechanism of neurogenesis in the DG can hold therapeutic implications for AD and other neurodegenerative disorders. Brain Derived Neurotrophic Factor (BDNF) is important in the generation and maintenance of neurons; and it activates the Transient receptor potential canonical (TrpC) channel. TrpC channels are found within the DG, which is a known area of continual neurogenesis. To understand BDNF’s neurogenerative mechanism, we designed a study that would allow us to determine the role of its downstream effector, the TrpC channel. We thus hypothesize that the neurogenerative effect of BDNF is through the TrpC channel. Resolving this hypothesis would lead to novel treatment options for AD and other neurodegenerative disorders. We tested whether SKF 96365, a TrpC channel blocker, is capable of blocking neurogenesis in the hippocampus. We treated postnatal day 9 rat hippocampal slices with SKF 96365 and Edu, a marker for new cell growth, for three days in vitro. In the DG, SKF treated cells showed a 40% decrease in neurogenesis compared to control conditions, indicating that TrpC channels are necessary for neurogenesis (p=.002). Future work is necessary to delineate the specific TrpC channel subtype involved, and eventually, the full mechanism of neurogenesis.
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**IN VIVO IMAGING OF ALPHAVIRUS INFECTION: VISUALIZING THE EARLY CNS INVASION USING NON-INVASIVE TECHNIQUE**

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**BACKGROUND:** Venezuelan equine encephalitis virus (VEEV) is a reemerging public health threat with no approved human vaccines within the United States. As a high containment threat and select agent, work with virulent VEEV must be performed in the ABSL-3. This has hampered research in the past and has made it difficult to utilize sophisticated equipment usually not available in a high containment laboratory. Therefore, we have focused on developing a challenge model with the vaccine strain of VEEV, TC83, which would allow us to simplify and speed up the process of studying VEEV pathogenesis. Accordingly, we have identified productive central nervous system (CNS) infection as an endpoint for our vaccine studies, in which the major scientific goal has been to prevent VEEV infection.

**METHODS:** Following intra nasal inoculation of C57BL/6 and ICR mice with TC83 virus expressing firefly luciferase gene we performed daily visualizations of the viral infection utilizing intra peritoneal injection of luciferin. RESULTS: Daily imaging resulted in confirmation of early infection of the nasal cavity following invasion of the CNS by day 3. CNS infection was visualized for a following 6 days with no significant change in weight or temperature in the persistently infected mice. CONCLUSIONS: Our identification of an infection model similar to VEEV, utilizing the TC83-Luciferase virus, will assist in elucidating the encephalitic pathogenesis seen in human patient infections. The utilization of an in vivo imaging system (IVIS) combined with the genetically modified TC83 strain we created, will assist with vaccine protection analysis through rapid visual confirmation of viral invasion of the CNS. This process does not require sophisticated biocontainment space, select agent permits, sacrificing animals, or processing tissues while providing the possibility to repeatedly collect data from a single individual animal along with precise identification of the timing of CNS infection.

**Poster 64**

**SHAPE EFFECTS ON REFLEXIVE SPATIAL SELECTIVE ATTENTION**

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The process of attention works to filter the vast amount of information in an effort to use the brains limited resources for information that it deems to be most important for the task at hand. The basic paradigm for reflexive spatial attention involves presenting the subject with a stimulus, called a cue, in one of two spatial locations. After a short delay, on the order of msec, the target stimulus is presented. The subject is asked to press the button on the side of the target stimulus as quickly as possible. It has been previously shown that when a behaviorally irrelevant cue is presented before a target, it may either facilitate or inhibit the speed of target processing (reaction time) depending upon the spatial location, delay between cue and target (CTD), and the shape. When the CTD is shorter a facilitation of attention is seen; while a longer CTD produces an inhibition of attention. It has also been found that when the cue is the same shape as the target, reaction times are significantly slower for shorter CTD’s. The shape effect can be explained by the phenomenon of repetition suppression that has been seen in the Anterior Inferotemporal Cortex (AIT) and Lateral Intraparietal Cortex (LIP). Using physiological data these areas have been shown to encode shapes and based on these encodings, similarities between shapes have been defined. We hypothesized that if cue and target have similarly encoded shapes, then a larger repetition suppression will be produced, and thus a larger shape effect will be seen. As expected similarly encoded shapes produced slower reaction times. Repetition suppression could be driving these slower reaction times. Future research could attempt to determine which area might be driving these effects.
A single neuron can receive thousands of excitatory and inhibitory electrical inputs in the form of ions entering the cell through both ligand and voltage gated ion channels. Integration of these inputs can manifest into substantial variation of action potential firing rate and neural activity through the course of normal CNS function. In order to maintain an optimal level of excitability for the neuron to effectively process and store information, intrinsic signaling mechanisms exist in individual neurons that broadly modulate these electrical inputs throughout the entire neuron. In order to maintain a basal level of excitability in response to stimulus and in turn optimize firing rate, neurons regulate surface neurotransmitter receptors, synaptic density, and additional components. This process has been termed homeostatic plasticity. We are currently investigating Protein Phosphatase 1 mediation of homeostatic plasticity. Dephosphorylation of synaptic substrates by PP1 has previously been shown to play a critical role in reducing synaptic efficacy in order to induce long term depression (LTD) at individual synapses. Our experiments examine the role of PP1 in homeostatic downscaling of synaptic and extra synaptic electrophysiologic inputs. In response to a large and prolonged increase in neuronal activity (EPSP and subsequent action potential rate), PP1 dissociates from regulatory protein Inhibitor-2 and scales down excitability through dephosphorylation of synaptic scaffolding proteins, neurotransmitter receptors, and voltage gated ion channels. Dephosphorylation of these substrates serves to reduce overall surface neurotransmitter receptors (AMPAR) and increase outward potassium conductance, effectively reducing neuronal excitability and stabilizing firing rate. Understanding PP1 regulation in homeostatic plasticity is important in order for us to understand and effectively treat clinical manifestations of neural network instability that may arise from dysfunction in the endogenous maintenance of electrophysiologic homeostasis. These disorders include Epilepsy and Schizophrenia as well as Autism, where dysfunction in the intrinsic maintenance of network integrity during development may play a key role in the genesis of the disorder.

Colon cancer is the second most common cause of death from cancer in the U.S. This places a high value on the investigation of novel drugs that could serve as additional treatment options for this disease. Gamma secretase inhibitors (GSIs) are a class of drugs that have been shown to decrease proliferation in the small and large intestine; therefore, they may be useful in anti-cancer therapy. GSIs function by inhibiting the Notch pathway, a signaling pathway that controls cell fate in the intestine by directing progenitors to give rise either to absorptive or secretory cells. Notch suppresses the transcription factor Atonal Homolog 1 (Atoh1), which the Shroyer lab has shown to be a tumor suppressor. Our hypothesis is that GSIs exert their anti-proliferative effect by increasing expression of Atoh1. We obtained tissue sections from the intestines of mice treated with GSI. These mice were either Atoh1 knockouts or wild types, and some also had the APCmin genotype, which causes spontaneous intestinal polyp formation. These sections were stained via immunohistochemistry and assessed for proliferation, cellular differentiation, and apoptosis. In addition, we treated several human colon cancer cell lines with GSI and examined mRNA expression with real-time PCR. GSI decreased proliferation and increased secretory cell counts both in healthy intestinal tissue and in polyps from Atoh1-wild type mice, but not in Atoh1 knockouts. Tissue from Atoh1 knockouts displayed no secretory cell types and proliferation and differentiation in these tissues were not affected by GSI treatment. We found no GSI effect on apoptosis in either wild type or Atoh1 mutant tissue. rtPCR analysis showed that GSI increased expression of Atoh1 in cell lines in which the Shroyer lab had previously found GSI to cause a reduction in proliferation. Our results indicate that Atoh1 expression is integral to the reduction in proliferation seen in GSI treatment. Future research into Atoh1 as a drug target may lead to new options in colon cancer therapy.
BK VIRUS AS A POTENTIAL COFACTOR IN CERVICAL CANCER
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Background: Cervical cancer is the third most common type of cancer in women worldwide. Nearly all cases of cervical cancer are caused by a persistent human papillomavirus (HPV) infection. The human papillomavirus is a non-enveloped, ds-DNA virus. There are approximately 40 types of HPV which have been found to promote cellular transformation, of which 15 are classified as high-risk for developing cervical intraepithelial neoplasia. The BK polyomavirus is also a non-enveloped, ds-DNA virus, which was first discovered in urine from a renal transplant recipient. Following a primary upper respiratory infection, the BK virus establishes latency nearby cervical tissue in the urogenital tract. Many studies have established the role of BK virus in renal transplant rejection and the development of urogenital carcinomas. Both the human papillomavirus and BK virus have been found to induce cellular transformation by uniquely inhibiting p53 and Rb, crucial tumor suppressor genes through two different pathways. Considering the nature of the BK virus infection and its large T-antigen interactions, the BK virus may cooperate synergistically with HPV to drive the development of cervical cancer. Objective: To examine the relationship between the BK virus and HPV infection in human cervical specimen. Methods: For this study over 200 HPV positive and negative cervical samples were tested for the presence of BK virus using real-time, quantitative PCR. Results: We discovered 4 BK positive among the HPV positive samples, and 12 BK positive among the HPV negative samples. Conclusions: To our knowledge we are the first to detect a co-infection of BK and HPV viruses. Although this study did not reveal a significant correlation between BK and HPV positivity, it is premature to rule out the possibility. Furthermore, this study warrants further testing of cervical specimen to examine the relationship between BK and HPV co-infection and cervical cancer.

OVER-EXPRESSION OF AUTOCRINE PROGASTRIN UP-REGULATES DCAMKL+1 AND CD44 POSITIVE STEM/PROGENITOR CELLS, ASSOCIATED WITH SURPRISING TRANSFORMATION OF HEK-293 CELLS, IN VITRO AND IN VIVO
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In recent years we have demonstrated that progastrin peptide (PG) exerts anti-apoptotic and proliferative effects on normal and cancerous epithelial cells, in vitro and in vivo, and increases the risk of colon carcinogenesis in transgenic mice overexpressing PG. In vivo studies with PG overexpressing hGAS mice suggest that there is an increase colonic crypt cells positive for DCAMKL+1 and CD44. It is, however, not known if progastrin can directly induce an increase in the number of stem/progenitor cells, in vitro, and if this change is translated into a possible increase in clonogenicity/tumorigenic/metastatic behavior of cells. We therefore used the progastrin responsive HEK-293 cells, which are incompletely transformed with negligible clonogenic/tumorigenic potential. Mutant-hGAS-HEK293 clones (HEK-PG) were generated and confirmed to overexpress full-length PG. A significant increase in proliferation of HEK-PG vs HEK-C cells (control) was measured in vitro. Cells, stained for putative stem cell marker (DCAMKL+1)/progenitor cells marker (CD44), was examined by fluorescent confocal microscopy and quantified by Western Blot analysis. Expression of DCAMKL+1/CD44 increased 2-3 fold in HEK-PG clones vs HEK-C clones, suggesting, for the first time, that progastrin directly enhances the number of stem/progenitor cells. Significant increase in DCAMKL+1/CD44 cells was confirmed in colonic crypts of Fabp-PG mice, overexpressing PG in colons. The most surprising finding was that overexpression of PG in HEK-PG clones imparted a clonogenic/tumorigenic/metastatic potential to the cells, in vitro and in vivo. However, IEC-18-PG clones were not rendered clonogenic/tumorigenic, suggesting that overexpression of PG in the background of HEK-293 cells, represented the second hit required for transformation. IEC-18 cells are immortalized but apparently lack the first hit and thus remain non-transformed in the presence of progastrin expression. In addition, we have measured the activation of two transcription factors, NFκB/β-catenin, in response to PG, which likely translates into the transforming second hit in response to autocrine PG expression in pre-initiated cells. Since a large percentage of GI cancers express autocrine PG, down-regulation of PG and/or its receptor (Annexin2), and/or its mediatory signaling pathways should prove to be a powerful method for reducing stem cell/progenitor cell populations and attenuating tumorigenic/metastatic potential of the cancer cells.
Adult patients with acute lymphoblastic T cell leukemia (T-ALL) have a very poor prognosis and few effective therapeutic options. Therefore, novel therapies that increase the efficacy of the treatments and that prolong T-ALL patient survival are needed. Malignant T cells require high concentrations of nutrients to sustain their increased rate of proliferation. In particular, the levels of the non-essential amino acid L-Arginine are fundamental for malignant T cell proliferation and survival. In this study, we determined whether L-Arginine depletion by the pegylated form of the L-Arginine-metabolizing-enzyme arginase I (peg-Arg I) impairs the proliferation of malignant T cells. Our results show that peg-Arg I depletes L-Arginine levels in vitro and in vivo. In addition, treatment of malignant T cell lines with peg-Arg I significantly impaired their proliferation, which correlated with an arrest in the G0-G1 of the cell cycle, followed by the induction of apoptosis. Induction of apoptosis was observed through increases in Annexin V positive cells and active caspase 3, a release of cytochrome c from the mitochondria into cytosol and a decrease in BCL-2. Furthermore, peg-Arg I impaired the expression of cyclin D3, a fundamental protein in T-ALL proliferation, through a global arrest in protein synthesis. Injection of peg-Arg I plus chemotherapy agent Cytarabine prolonged survival in mice bearing T-ALL tumors. This anti-tumoral effect correlated with an inhibition of T-ALL proliferation in vivo, a decreased expression of cyclin D3, and T-ALL apoptosis. In conclusion, Peg Arg I therapy could potentially be used in the future as a tool in the fight against T-ALL.

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 or a constitutively active ligand-independent form of IGF-IR, development of mammary hyperplasia and palpable tumors occurred. In addition, 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 tumors in the breast is not known. SOCS2 is a novel gene target of IGF-1 signal transduction identified by microarray in our lab. SOCS2 was shown to be repressed at 3 hours after IGF-I treatment in MCF7 cells, and this was validated via qPCR. The repression of SOCS2 by IGF-I was inhibited by pretreatment with IGF-IR inhibitors, suggesting that the repression of SOCS2 is specific to IGF-I signaling. Mechanistically, IGF-I appears to repress SOCS2, in MCF7 cells, at the level of transcription and not by causing instability of SOCS2 mRNA. In addition, SOCS2 has previously been shown to inhibit STAT5 and prevent its activation. We have shown that IGF-1 stimulation of MCF7 cells leads to phosphorylation of STAT5 and this IGF-1-induced phosphorylation can be inhibited by over-expressing SOCS2 in vitro. In addition, preliminary evidence by ChIP assay and an siRNA experiment suggests that the transcription factor FOXA1 may be involved in the repression of SOCS2 by IGF-1. In summary, we show that SOCS2 is a novel gene target of IGF-I signaling and is repressed by IGF-I stimulation in MCF7 breast cancer cells. Furthermore, the IGF-1-mediated repression of SOCS2 appears to be occurring at the level of transcription, potentially involving FOXA1. In addition, the repression of SOCS2 by IGF-1 may lead to an increase in IGF-1-induced STAT5 phosphorylation. Together, this suggests that SOCS2 is a direct gene target of IGF-I signaling and that ability for IGF-I to repress SOCS2 may be a crucial event that plays a role in driving the development or progression of breast cancer.
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AN INSTITUTIONAL REVIEW OF OUR EARLY EXPERIENCES WITH NIPPLE SPARING MASTECTOMIES AT THE GEORGE WASHINGTON UNIVERSITY
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Background: Surgical technique in treating breast cancer has evolved to allow preservation of breast skin with little to no added oncologic risk and improved cosmesis. The most recent advance, the nipple-sparing mastectomy (NSM), allows patients with certain tumor characteristics to preserve their native nipple areola complex (NAC). Objective: The purpose of this study is to measure the oncologic and cosmetic outcome in our initial NSM cohort, selected by practice guidelines set forth in the NSM literature. Methods: Sixteen NSMs with immediate reconstruction were performed in eleven consecutive women (mean age 44.5) by dedicated breast surgeons from August 2007 to December 2009. NSM was performed for prophylaxis in the setting of atypia or LCIS (n=9), infiltrating ductal carcinoma (n=4), or ductal carcinoma in situ (n=3). Patients were candidates for this procedure if they had peripheral tumors that were more than 2cm from the NAC, less than 3.5cm and with no gross nipple involvement or inflammatory changes. Neoplastic nipple involvement was defined as any intraoperative or permanent pathologic report of atypical or malignant cells in the excised subcutaneous nipple bud. Data was collected to determine oncologic and cosmetic results with a mean follow-up of 15 months. Results: Of the sixteen NSMs, two nipple buds (12.5%) were found to have atypia or neoplastic involvement on intra-operative frozen section, prompting conversion to skin-sparing mastectomy. Nine NSMs (64.3%) retained complete viability of the NAC. Five NSMs (31.3%) experienced partial necrosis of the NAC, of which two (12.5%) required operative debridement. Eight of the eleven patients rated their cosmetic satisfaction as good-to-excellent. To date, there has been no recurrence in this cohort of patients. Conclusions: Our experience demonstrates that at institutions performing low volumes of NSM, acceptable results can be obtained by careful adherence to the well-established pre-operative tumor criteria published in the literature. We encourage centers with experience in other mastectomy techniques to adopt this protocol.

Poster 72
TYROSINE KINASE INHIBITORS EFFECTS ON RENAL CELL CARCINOMA MIGRATION AND INVASION
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Renal cell carcinoma (RCC) is the most common malignant tumor of the kidney, accounting for 90% of all renal cancers. Up to 25% of newly diagnosed RCC patients have metastasis at presentation, and about 40% treated initially for localized disease have recurrence. Conventional cytotoxic chemotherapy has shown little or no anti-tumor activity against RCC, and to date has no role in either adjuvant or a neo-adjuvant therapy. Up to 80% of sporadic cases of RCC have been shown to manifest biallelic loss or inactivation in the von hippel lindau (VHL) gene. Loss of this gene results in an accumulation of HIF-1α transcription factor, which has been shown to drive RCC tumor genesis through the activation of multiple tumor promoting survival signaling cascades (VEGF/mTOR/Raf). Elucidation and characterization of the VHL-HIF-Survival axis has now translated into the development of novel agents with improved clinical responses for the treatment of RCC (such as temsirolimus, sunitinib and sorafenib). These compounds have been shown to modulate the mTOR, VEGF/PDGF, and Raf/MEK/ERK signaling cascades, which have been shown to mediate cancer cell invasion and metastasis, thereby highlighting the importance of these drugs in preventing RCC progression. Wound Scratch assays and Matrigel Invasion assays were conducted using TK inhibitors, sunitinib and sorafenib on three different cell lines responsive to this therapy: 786O, A498 and ACHN. Migration inhibition was seen in all RCC cell lines with sorafenib and sunitinib, in a dose- and time-dependent manner. Matrigel Invasion assays demonstrated inhibition across all cell lines with both TK inhibitors. Sorafenib demonstrated greater inhibition of migration and invasion compared to Sunitinib, potentially due to Sorafenib’s mechanism of action, inhibiting more intracellular tyrosine kinases including the Raf and Akt pathway. This supports the blockade of VEGF/PDGF and Raf/MEK/ERK signaling cascades inhibiting migration and proliferation of RCC. Further research would involve testing in xenogeneic orthotopic nude mouse models to determine the effect of TKi and mTORi effect on metastatic spread. With this research we hope to establish proof-of-principle that will guide potential adjuvant and neoadjuvant clinical trials to the benefit of these cancer patients.
**Poster 73**

**IDENTIFICATION OF ATM PHOSPHORYLATION SITES AND RAP 1 INTERACTING FACTOR 1 (RIF1) BINDING SITES ON DEAD BOX 1 (DDX1) PROTEIN**

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DDX1 is part of the DEAD box protein family, a group of putative RNA helicases. DDX1 is both amplified and overexpressed in a subset of retinoblastoma, neuroblastoma, and alveolar rhabdomyosarcoma tumours and is believed to play a role in tumorigenesis and tumour progression. Following treatment with ionizing radiation, DDX1 accumulates into distinct foci, called ionizing radiation induced foci (IRIF). These foci colocalize with phosphorylated ATM protein kinase at DNA double strand break (DSB) sites and DDX1 can be phosphorylated by ATM in vitro. These results suggest that DDX1 may play an integral role in the ATM pathway as part of DSB repair. Co-immunoprecipitations with anti-DDX1 antibody have revealed an interaction between DDX1 and the DNA damage response protein, RIF1. Confocal microscopy has shown that RIF1 forms IRIF that colocalize with DDX1 IRIF. Furthermore, the formation of DDX1 IRIF is RIF1-dependent, indicating that DDX1 and RIF1 are interacting during DSB repair. To further elucidate the role of DDX1 in the damage response, I investigated its interactions with both ATM and RIF1. The goal of my first project was to identify which of five putative phosphorylation sites on DDX1 (Ser-269, Thr-278, Ser-362, Ser-377, and Ser-671) is targeted by ATM. Using site-directed mutagenesis, two full-length DDX1 constructs were generated (with either the Ser-269 and Thr-278 sites or the Ser-362 and Ser-377 sites mutated) and then subcloned into pGEX vector. GST-DDX1 fusion protein was purified from bacterial cells and will be tested using an in vitro ATM kinase assay. The goal of my second project was to identify the region of interaction between DDX1 and RIF1. Using PCR amplification, RIF1 was divided into four equal-sized fragments and subcloned into pGEX vector. GST-RIF1 fusion proteins will be tested for DDX1 interaction using a GST pull-down assay. Identifying the regions of interaction with ATM and RIF1 will shed light on the recruitment of DDX1 at sites of DSB, leading to a better understanding of the role of DDX1 and its link to cancer formation.

**Poster 74**

**FISH OIL: A NOVEL NATURAL PRODUCT WITH AN ANTI-DEPRESSANT-LIKE EFFECT**

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Background: Depression is a treatable common but serious illness that afflicts millions of people all over the world. Discovery of new antidepressants requires screening of potential compounds using animal models of depression such as the tail suspension test (TST) and the forced swimming test (FST). Limited studies on fish oil and omega-3 fatty acids have suggested antidepressant effects of these compounds. Objective: In our study we aim to investigate the effect of long-term administration of fish oil in mice using the standard TST experimental model. Methods: MF-1 strain mice were divided into 6 groups (n=48). Control groups were the saline (n=8) (0.2 ml), the fluoxetine (n=8)(10mg/kg) and the corn oil (n=8) (0.2 ml) groups. The rest of the groups were orally given fish oil at graded dose (n=8 each) (0.05, 0.1 and 0.2 ml). All groups received oral treatment for 28 days. Mice were subjected to the standard automated TST and immobility time variables were recorded and analyzed using one-way ANOVA (Post Hoc S-N-K). Results: Long-term daily administration of fish oil in mice leads to a significant decrease in immobility time in the Tail Suspension Test in comparison to the control groups (p<0.05). Such effects are significantly evident also at different doses (p<0.05). Conclusion: The results show that the long term administration of fish oil in mice leads to a decreased depressive-like behavior in TST. Future studies should emphasize on target pathways on which fish oil acts.
Background: Innervation of the respiratory system regulates respiratory patterns and maintains bronchomotor tone. This tone is controlled primarily by parasympathetic fibers traveling within the vagus nerve. Stimulation of muscarinic acetylcholine receptors in airway smooth muscle causes airway constriction. During lung transplantation, airway neural fibers are severed, and presumably, bronchomotor tone is absent. Consequently, inhaled anticholinergic agents, such as ipratropium bromide, would not be expected to elicit any bronchodilation. After lung transplantation, afferent airway reinnervation has been recently reported; however, efferent airway reinnervation has not been observed. Current knowledge concerning changes in airway function after nerve transaction is limited and the findings from this study may provide a better understanding of neural airway function. Objective: To assess cholinergic airway response in lung transplant patients with a recovered cough reflex by examining the airway response to inhaled ipratropium. Methods: Four patients who underwent lung transplantation greater than one year ago who were previously studied and found to have restoration of their sensory cough reflex were enrolled. Patients underwent baseline spirometry, lung volume measurements and high-resolution CT imaging of the lungs before ipratropium administration. Forty five minutes after ipratropium nebulization, repeat spirometry, lung volumes, and imaging were performed. Lung volumes were controlled for during repeat imaging. Pre- and post-ipratropium CT image airway diameters were measured and compared. Results: A total of 110 airways were measured. Airway diameters were divided into <5mm, 5-10mm and >10mm. The mean airway diameters before ipratropium administration for airways <5mm were 3.5 +/- 0.7mm, for airways 5-10mm were 6.6 +/- 1.3mm, for airways >10mm were 12.2 +/- 0.0mm. The mean post-ipratropium diameters for airways <5mm were 3.6 +/- 0.6mm, for airways 5-10mm were 6.8 +/- 1.5mm, and for airways >10mm were 12.1 +/- 0.0mm. The mean increase for all airways was 6.3 +/- 10.3%. In airways <5mm, there was a mean increase of 7.7 +/- 11.4%, for airways 5-10 mm, a mean increase of 6.1 +/- 10.1% and for those airways >10 mm, there was a mean decrease of 0.1 +/- 0.0%. p value is <0.05. Conclusions: In lung transplant patients with restoration of airway sensory function, a small increase in airway diameter after ipratropium administration was observed.

Poster 75
EFFECT OF IPRATROPIUM ADMINISTRATION ON AIRWAY DISTENSIBILITY IN LATE LUNG TRANSPLANT RECIPIENTS
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Poster 76
REPEATED INTERMITTENT TREATMENT WITH WAY 163909 INDUCES BEHAVIORAL TOLERANCE TO ITS ANORECTIC AND HYPMOTIVE EFFECTS
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The serotonin (5-HT) 5-HT2C receptor (5-HT2CR) is distributed widely throughout the corticolimbic circuit and negatively modulates its dopamine neurotransmission. 5-HT2CR dysfunction has been implicated in a variety of diseases, addiction included. 5-HT2CR agonists are a novel approach in restoring dopamine neurotransmission. However, repeated treatment with the non-selective 5-HT2CR agonist MK 212 induces behavioral tolerance, potentially due to desensitization mechanisms. The purpose of the present study was to further characterize the effects of repeated 5-HT2CR selective ligand exposure on behavior induced by acute agonist administration. Male, Sprague-Dawley rats were treated daily for 7 days with WAY 163909 (selective 5-HT2CR agonist, 10mg/kg), SB 206553 (selective 5-HT2CR inverse agonist, 4mg/kg), SB 242084 (selective 5-HT2CR antagonist, 1mg/kg), or vehicle (45% β-cyclodextrin) (n=10/group). Weights were recorded daily; 24 hrs following the last repeated treatment, animals were challenged with WAY163909 (10 mg/kg) or vehicle and locomotor activity was measured. Following locomotor analyses, animals were sacrificed and brain tissue was dissected and stored. Repeated administration of WAY 163909 produced an anorectic effect with delayed weight gain. Acute administration with WAY 163909 reduced total ambulations compared to vehicle controls (p<0.05, two-way repeated measures ANOVA). Repeated WAY 163909 administration blunted the decrease in ambulations induced by acute WAY 163909 challenge (p<0.05, two-way repeated measures ANOVA). Conversely, repeated treatment with SB 206553 or SB 242084 did not alter the behavioral response to acute WAY 163909 challenge. Thus, while repeated exposure to a selective 5-HT2CR agonist induced behavioral tolerance to the anorectic and hypomotive effects induced by 5-HT2CR agonist challenge, repeated administration of a 5-HT2CR inverse agonist or antagonist were without effect, indicating that alterations in 5-HT2CR function that may occur upon repeated exposure to these ligands does not interfere with agonist activation of the receptor. Several molecular mechanisms may underlie the observed 5-HT2CR functional desensitization, including reduced receptor isomerization, and receptor recycling. Studies investigating the 5-HT2CR protein expression profile in subcellular compartments from various brain regions in the corticolimbic circuit (e.g. prefrontal cortex, caudate putamen, nucleus accumbens) are ongoing.
**Poster 77**

**UPTAKE OF ESTRONE-SULFATE BY INSIDE-OUT VESICLES OF HUMAN TROPHOBLAST TISSUE**

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The breast cancer resistance protein (BCRP/ABCG2) is a member of the ATP Binding Cassette-Transporters and is highly expressed in human placenta. Placental BCRP is an important contributor to the efflux of xenobiotics from the apical membrane of the syncytiotrophoblast to the maternal circulation. Estrone-Sulfate (E1S) is the endogenous substrate of BCRP and has been used to investigate the in vitro activity of BCRP in various tissues. E1S is a circulating plasma estrogen that is hydrolyzed by steroid sulfatases (STS) to estrone (E1) and sulfate. The activity of STS was determined in several tissues including human placenta. The objective of this investigation is to determine the activity of human placental BCRP in the efflux of E1S. Inside-out vesicles (IOV) were prepared from brush border membranes of human placentas. The expression of BCRP was determined by western blot analyses. The ATP-dependant uptake of \(^{[3H]}\)-E1S was determined in presence of the sulfatase inhibitor STX 64 (Ki, 10nM). The uptake of \(^{[3H]}\)-E1S by the IOV ranged between 240 – 340 pmol.mg protein⁻¹.min⁻¹. However, the uptake was inhibited by inhibitors that are selective for other transporters as follows; BCRP (Ko143 [125nM]), 45%; P-gp (Verapamil [300μM]), 35%; and MRP (Indomethacin [200μM]), 80%. Therefore, our data indicates that multiple placental efflux transporters are responsible for the efflux of E1S in human placentas.

**Poster 78**

**A NOVEL REDOX MECHANISM-BASED THERAPEUTIC STRATEGY TO IMPROVE ANTICANCER ACTIVITY IN THE BCR-ABL-DRIVEN LEUKEMIA BY COMBINATION OF GLEEVEC AND REDOX-MODULATING AGENTS**

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Background: BCR-ABL fusion gene is the hallmark genetic abnormality observed in more than 95% of chronic myeloid leukemia (CML), and plays essential role in malignancy transformation. Specific oncoprotein kinase inhibitor Gleevec effectively suppresses the constitutive tyrosine kinase activity of BCR-ABL, and has been developed as the front-line agent for CML. However, clinical Gleevec resistance has developed and become a significant therapeutic challenge, most resulted from BCR-ABL mutations. The emergency of an alternative strategy to control BCR-ABL mutant cells growth is the current focus. Intriguingly, previous publications and our former study showed that BCR-ABL can induce cellular redox imbalance with the increase of reactive oxygen species (ROS). BCR-ABL-induced ROS has been identified to play crucial role in malignant transformation, oxidative DNA damage and gleevec-resistance. In this study, we indicate the potential to suppress CML by targeting this biological alteration with cellular redox modulation strategy. Objective: We postulate that targeting BCR-ABL-induced redox alteration by preferentially triggering excessive ROS-mediated cell death with exogenous ROS-generating agents, or by controlling the development of Gleevec-resistance with limiting the ROS generation machinery. These treatments will present the good combination effects on the sustained suppression of BCR-ABL-driven leukemia by Gleevec. Methods: Inducible BCR-ABL-expressing cell, and human CML cells use as study models. MTT cell proliferation assay, Annecin-V/PI cell death assay, cellular redox flow cytometry assay and protein immunoblot analysis were performed. Results: We identify glucose metabolism contributes to BCR-ABL-induced cellular ROS generation. Limiting glucose amount suppresses cellular ROS, and sensitizes the cell to Gleevec. Combination of a redox stress inducer, PEITC and Gleevec enhance and accelerate cell killing effects in CML cells. Importantly, we further showed that inhibition of BCR-ABL downstream survival factors could abrogate the ability of CML cells to tolerate oxidative stress and thus increase their sensitivity to ROS insults. Conclusions: Combination of redox targeting modulation and specific oncogenic inhibitors show promising cell killing effects and suppress the development of Gleevec-resistance in CML. This novel therapeutic strategy warrant further clinical investigation.
AUGMENTATION OF ASPIRIN EFFECTS BY CHOCOLATE
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BACKGROUND: In recent past, research has been done to elaborate the effects of flavonoids on platelets, but the role of chocolate as an augmenter of aspirin effects has not been brought into light in our part of the world. OBJECTIVE: Our aim was to establish the anti-platelet or aspirin like effects of flavonoid rich foods i.e. "Chocolate as an augmenter of aspirin functions. METHODS: This non-randomized quasi experimental study was conducted on 65 healthy adult volunteers including 27 males. Subjects included were healthy, non-smoking, 20-30 years old adults, with no blood dyscrasias. Subjects with chronic liver disease, arterial hypertension, ischemic heart disease, taking hormonal, calcium and vitamin supplements, pregnant and estrogen taking women were excluded from the study. Health of subjects was evaluated by a questionnaire. Subjects were divided into two groups, a control group which consumed 100mgs oral aspirin and an interventional group consuming 100mgs oral aspirin and 18.75gms of dark chocolate (flavonoid rich). The Bleeding time estimation of both the groups was done by trained lab professionals, who were blinded of the nature of the study; utilizing the Duke Method of bleeding time estimation before and after consuming the drug in case of the control group and drug along with chocolate in case of the interventional group.

RESULTS: Data was analyzed by SPSS 15.0. First bivariate analysis was done by comparing the means of both the pre-test groups i.e. before consumption of aspirin and also before consumption of chocolate and aspirin together through independent t-test in which we found a insignificant p- value (p=0.798) which showed that both the groups were similar before the intervention. The bleeding time of both post test groups i.e. groups after consumption of aspirin & also the group after consumption of aspirin and chocolate were again analyzed by the same procedure as described above. Independent t- test showed a highly significant p-value (p=0.006) which shows that our intervention i.e. chocolate has increased the effects of aspirin in comparison to when aspirin was used alone. Furthermore multivariate regression models were also used which gave an R² value of .250. CONCLUSION: Chocolate has a significant role in augmenting the anti-platelet effects of aspirin. However, study was conducted for a short period of time therefore it can only measure the short term effects of chocolate consumption on aspirin effects.

INFLUENCE OF SALBUTAMOL ON BRONCHOCONSTRICTION IN SWIMMERS AFTER EUCAPNIC VOLUNTARY HYPERPNOEA
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BACKGROUND: Eucapnic voluntary hyperpnoea (EVH) test is recommended by the International Olympic Committee Medical Commission (IOC-MC) to confirm exercise-induced bronchoconstriction (EIB) in athletes. We previously showed that 78% of elite swimmers had bronchoconstriction post-EVH test, probably partly due to irritative effects of chlorination products in their airways. Respiratory irritants, such as organic dust or nitrogen dioxide, have been shown to be associated with reduced bronchial response to β2-agonist drugs. Repeated inhalation of chlorine derivatives by swimmers could also alter the bronchial response to β2-agonists.OBJECTIVE: Our objective was to determine the effects of a short-acting β2-agonist (salbutamol) on response to a 6-minute EVH test in elite swimmers.METHODS: During the same week, 18 elite swimmers performed two 6-minute EVH tests, separated by a period of at least 48 hours. Subjects inhaled 200µg of salbutamol (T1) or placebo (T2), following a double-blind randomization. Forced expiratory volume in one second (FEV1) was measured at rest, 10 minutes after inhalation of salbutamol or placebo and every 5 minutes for 30 minutes after the EVH test. Hyperpnoea induced bronchoconstriction (HIB) was defined as a fall of 10% or more in FEV1 after the EVH test.RESULTS: FEV1 at rest was similar at T1 and T2 (mean±SD:114±15% and 114±13% respectively, p=0.71). The mean increase in FEV1 after salbutamol or placebo inhalation was 7±4% and -1±2%, respectively (p<0.0001). Maximum FEV1 fall post-EVH was 5±3% at T1 and 10±4% at T2 (p=0.0004). Swimmers with HIB (n=8) had a lower baseline FEV1 compared with swimmers without HIB (108±12% vs 122±13%, p=0.04), and an higher FEV1 fall post-EVH at T2 (14±2%) compared with swimmers without HIB (7±2%) (p<0.0001). Change in FEV1 fall between T2 and T1 was significantly different in swimmers with HIB (7±4%) compared with swimmers without HIB (2±3%) (p<0.0001).CONCLUSION: Inhalation of salbutamol prevents occurrence of light bronchoconstriction in elite swimmers with HIB despite a repeated exposure to chlorine derivatives.