BETTY AND GUY BEATTY CENTER FOR INTEGRATED RESEARCH

INOVA HEALTH SYSTEM

FOURTH ANNUAL RESEARCH REPORT 2009

INOVA® RESEARCH CENTER

INOVA® HEALTH SYSTEM

Acknowledgements:

We would like to thank Deena Hallaji from the Betty and Guy Beatty Center for Integrated Research for her excellent work organizing this annual report as well as Anne Doyle from Inova's Marketing Communications/Photography who did an outstanding job providing photos.

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MESSAGE FROM THE EXECUTIVE DIRECTOR OF RESEARCH INOVA HEALTH SYSTEM

In 2009, research remained an important priority at Inova Health System. Several new initiatives, undertaken throughout the year, strengthened our research infrastructure at the Betty and Guy Beatty Center for Integrated Research, Inova Health System. Researchers investigating cancer, liver disease, obesity, advanced lung disease, atrial fibrillation and neurosciences continued to show tremendous academic productivity as a result of the progression of each research team, their collaborative efforts, and the institutional support provided to the teams.

Additionally, Inova's investigators and leadership demonstrated increased interest in translational research and personalized medicine. These efforts are being undertaken through collaborations with partners such as George Mason University, Ignite Institute, and other biopharmaceutical companies. Initiatives of this kind promote our research goals for developing cutting-edge, investigator-initiated research protocols, a research biorepository, and the implementation of personalized medicine protocols. These combined efforts are focused on our vision of becoming one of the best healthcare systems in the world.

Finally, over the past year, Inova has implemented several mechanisms that directly support and encourage research throughout the system. For example, in addition to supporting the office of research and each of our research teams, Inova provided research funding to encourage innovative and patient-centered research projects. Inova's faculty grants, research seed grants, and summer student grants have been excellent venues for providing start up funds for promising faculty and innovative projects. Additionally, in 2009, Inova's leadership established a new “George Mason-Inova Life Sciences Fund" to encourage collaborations among investigators from the two institutions. These research funds have engendered enthusiasm for original and productive research among our faculty and students.

Finally, to further strengthen our research infrastructure, Inova has elicited recommendations from Deloitte consulting. Their input will help optimize the research infrastructure within our research hub as well as our strategically-focused research programs. By coupling these research efforts with Inova's plans for developing robust electronic health records, information technology and informatics infrastructure our investigators will have an excellent opportunity to carry out projects involving health services research and translational research concerning several important chronic diseases. I am confident that each year we will grow closer to the full realization of a solid research infrastructure and our vision of becoming one of the best health care systems in the world.

Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF
Executive Director of Research, Inova Health System
Professor of Medicine, Virginia Commonwealth University, Inova Campus
Affiliate Professor of Biomedical Sciences, George Mason University

CENTER FOR INTEGRATED RESEARCH
INOVA HEALTH SYSTEM

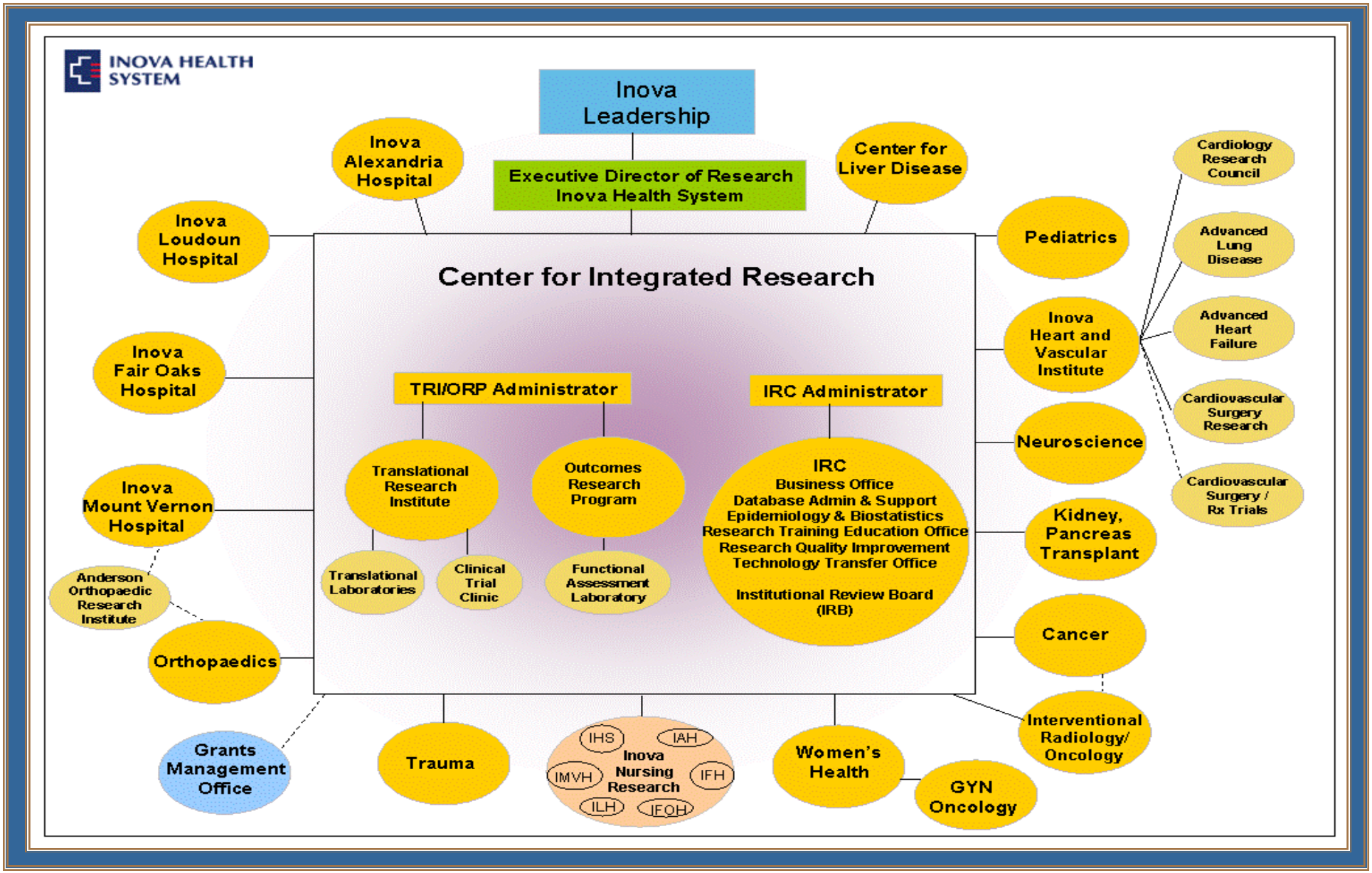
Since the opening of the Betty and Guy Beatty Center for Integrated Research at Inova Health System in 2008, the center has focused on providing an integrated and efficient research infrastructure for our investigators. The center was designed to bring together the research administrative offices with those units involved in the implementation of research. The administrative offices oversees the business aspects of research as well as the administrative offices of the Institutional Review Board(IRB), TechnologyTransfer, Research Contracting,and Research Training and Education.

Additionally, the center houses the Translational Research Institute (TRI) with its laboratories, research bio-specimen banking facility, and outpatient clinical trial area. The TRI labs have the capacity to utilize gene expression technologies, ELISA-based protein assays, as well as the upcoming cell culture facility. These technologies are used extensively for biomarker validation as well as implementation of novel clinical trial and personalized medicine protocols. These labs are jointly staffed by Inova and collaborators from George Mason University (GMU).

The research bio-specimen banking facility of TRI is specifically designed to house twenty -80^0 C freezers in a temperature controlled environment with backup electricity and a sophisticated electronic freezer temperature monitoring system. Currently, over 19,000 specimens from Center for Liver Diseases patients are stored in six freezers. Other research teams who have purchased freezers to accommodate their specimen needs include the Advanced Lung program, Cardiac Surgery program, Cancer program, and the Neurosciences/Trauma program. All freezers are centrally monitored to assure that research specimens are stored at optimal temperatures to provide important quality control for specimen integrity.

The third component of the Center for Integrated Research (CIR) is the Outcomes Research Program with its functional assessment laboratory. This laboratory is designed to implement research protocols that assess activity of daily living and other functional assessment measures of patients with chronic diseases.

Since November of 2008, the Betty and Guy Beatty Center for Integrated Research at Inova Health System has been fully operational, providing cutting-edge, patient-oriented research benefiting Inova's patients and investigators. The center will continue to grow and play a pivotal role in supporting Inova's research mission and vision to become the best healthcare system in the world.


INOVA HEALTH SYSTEM
Inova Leadership
Executive Director of Research
Inova Health System
Inova Alexandria Hospital
Center for Liver Disease
Inova Loudoun Hospital
Center for Integrated Research
Inova Fair Oaks Hospital
TRI/ORP Administrator
IRC Administrator
Inova Mount Vernon Hospital
Translational Research Institute
Outcomes Research Program
IRC
Business Office
Database Admin & Support
Epidemiology & Biostatistics
Research Training Education Office
Research Quality Improvement
Technology Transfer Office
Institutional Review Board (IRB)
Translational Laboratories
Clinical Trial Clinic
Functional Assessment Laboratory
Anderson Orthopaedic Research Institute
Orthopaedics
Grants Management Office
Trauma
IHS
IAH
IMVH
Inova Nursing Research
IFH
ILH
IFOH
Women's Health
GYN Oncology
Pediatrics
Inova Heart and Vascular Institute
Neuroscience
Kidney, Pancreas Transplant
Cancer
Interventional Radiology/ Oncology
Cardiology Research Council
Advanced Lung Disease
Advanced Heart Failure
Cardiovascular Surgery Research
Cardiovascular Surgery / Rx Trials

The Center for Integrated Research serves as the hub for the decentralized research conducted across Inova Health System. The Research Hub supports all Research Spokes (Research Teams) and researchers from Inova Health System. The administrative component of the Center for Integrated Research or Inova Research Center (IRC) consists of the Business Office, IRB Administrative Office, Research Training and Education Office, Research Quality Improvement Team, Technology Transfer Desk and Contracting, Database and Support, as well as Epidemiology and Biostatistics Office. The IRC team of professionals provides support to members of the research spokes by ensuring all federal, state, and local rules are followed to generate quality research results that benefit patients, families, and the organization.

In 2009, our research activities increased as indicated by the number of research applications submitted to the IRC and the IRB. This is due in part to continuous support from Inova's senior leadership. The following pages provide summaries of the activities for each of the IRC offices to highlight the continuous support offered by the IRC team to our investigators.

The IRC is managed by Gity N. Porjosh, MPH, and supported by Terry Castro-Perez, Sr. Administrative Assistant.

RESEARCH BUSINESS OFFICE

In 2009, the Business Office continued its support to the research spokes with various financial matters required to conduct research studies. Many of these routine activities concerned budgeting, financial reporting, processing research invoices, and developing study matrices. Special attention has been given to research billing compliance this year. This effort was overseen in conjunction with the Compliance Department to develop a process that flags research bills within the financial system. Furthermore, the review process ensures bills are appropriately assigned to payers. The process integrates efforts of the research spokes, financial systems, and business office to effectively review and flag research financial records.

The Business Office continuously strives to streamline its processes and operations to efficiently and effectively provide support to the research spokes. On a monthly basis, program managers review financial results, which are prepared by the Business Office and include year-to-date and cumulative statistics. Additionally, matrix reviews are conducted prior to the start of research studies to ensure quality data entry for capturing research activities impacting study specific revenue and expenses. Variance reporting was introduced to the spokes to better track the expenses of the studies and the administrative cost centers.

In 2009, the Business Office worked with Inova Fairfax Hospital leadership to redesign the pillar report to include both budget and actual statistics for comparison by spoke program manager and administrators. Also, the Business Office has worked with Corporate Accounting to enhance the project accounting reports from Oracle Discoverer.

The Business Office team consists of Candy Conway, MBA, and Camilo Naval, MMBM. They oversee routine activities and support spokes' research operations by also providing guidance regarding the purchase of capital equipment and other business functions.

INSTITUTIONAL REVIEW BOARD (IRB) ADMINISTRATIVE OFFICE

The goal of the Institutional Review Board is to ensure compliance with the mandates of the Federal Office of Human Research Protection. Inova provides research investigators with two mechanisms to review and support research protocols throughout the Inova Health System: two local Institutional Review Boards (IRB) and the centralized Western IRB. The local boards (Groups A & B) are independent and supported by the IRB Administrative Office. The Western IRB is supported by a Program Manager liaison at Inova.

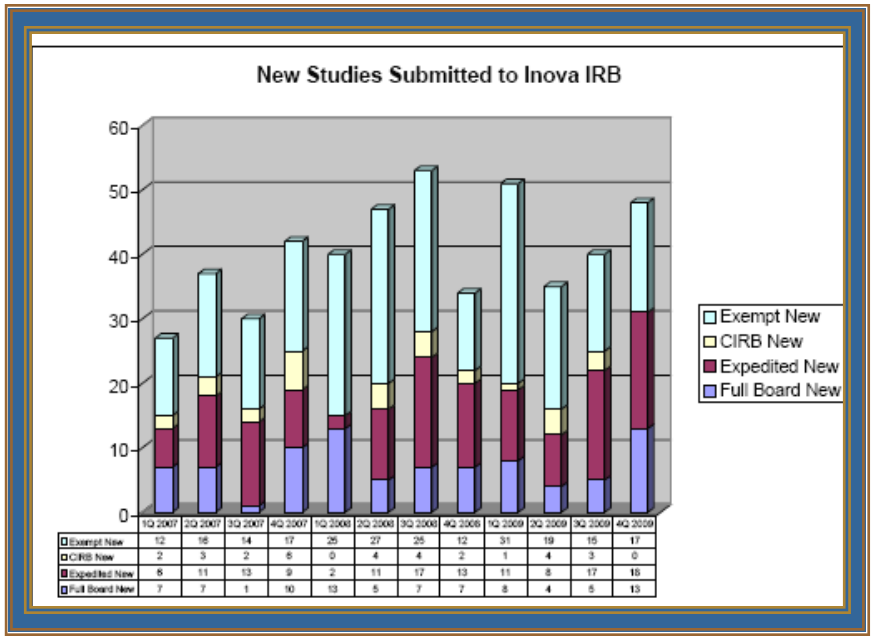


Figure 1

In 2009, IRB Group A had 49 full board reviewed studies, 42 closed to accrual, and 64 expedited reviews. IRB Group B had 57 full board reviewed studies, 50 closed to accrual, and 60 expedited reviews. NCI CIRB had 39 open studies with Inova PI, and WIRB had 78 open studies for a total of 439 nonexempt open studies for 2009.

In 2009, the (IRB) had 106 open studies requiring approval and renewal by a full board. An additional 163 assigned studies were reviewed and renewed on an expedited basis. The IRB manager who is a member of both Group A and Group B boards completes expedited reviews. In addition, while the exempt studies do not require IRB oversight, they must be reviewed for an initial determination of the "exempt" status. There were 82 exempt studies reviewed by the IRB manager and staff in 2009.

In addition to these studies, Inova investigators participate in 39 federally -sponsored oncology studies that have oversight provided by the NCI Central IRB (CIRB). A designated IRB member (usually the IRB chair) performs an initial review of each study. All consents as well as an amendment or renewal for these studies are initally reviewed by the IRB manager and staff to assure the Inova required consent elements are met.

In 2009, 174 new studies were reviewed by the Inova IRB. About 15% of submitted studies are deemed more than minimal risk and require full IRB approval. Approximately half of the studies reviewed by the IRB involve human subjects, but they are determined to be exempt from IRB approval and exemption certificates are issued. Figure 1 shows trends in the new research submissions over a 3-year period. As indicated, submissions have increased as research becomes more entrenched in the clinical programs across the Inova Health System.

Because investigators and research personnel are required to have human subject research training, Inova Health System began to offer the web-based Collaborative IRB Training Initiative (CITI) in 2007 as an alternative. The Executive IRB Committee has decided that effective December 31, 2009, all Inova researchers and research personnel involved in human subjects research are required to complete the CITI human subject research training program before receiving approval for any research protocol. Certification is effective for three years. Since Inova began this process, 642 human subject research training certificates have been completed, 445 of these certificates were completed in 2009.

The IRB Administrative Office ensured all policies were up-to-date and maintained per regulations as well as the forms used by researchers for submission to the board. A number of federal-wide assurances were established with non Inova employeed physicians conducting research at Inova Health System.

The IRB Administrative office consists of Laura Miller, MHSA, CLP (IRB Manager), Suzanne May, MPH, CLP, Kathy Ankrah, BS,CHEP, and BJ Pulsipher, RN (part-time). Michael Sheridan is the chairman of local boards.

WESTERN INSTITUTIONAL REVIEW BOARD (WIRB)

The Western Institutional Review Board (WIRB) serves as the centralized commercial review option for research investigators. Funded industry-sponsored studies are reviewed through WIRB with an Inova Program Manager serving as the program liaison to Inova investigators.

In 2009, approximately 78 studies were opened with the WIRB. The local IRB continues to maintain records of all WIRB studies, as well as changes in the research protocol and adverse events. This year, WIRB adjusted their fee schedule and revised submission forms to reflect process changes for reviewing multi-center studies. All Inova study staff who work with WIRB were informed of these changes via email, the Spoken News, and IRB webpage updates. An internal tracking document is continually updated to monitor questions from Inova and study sponsors, as well as the responses received from the WIRB.

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This tracking system is used to update the frequently asked questions (FAQ) file for research coordinators. The FAQ is currently available on the IRC share drive and the IRC webpage, to assist coordinators in preparing WIRB submissions and responding to queries from sponsors.

Post Approval Monitoring

In July 2009, the Executive IRB Committee implemented a new IRB post approval monitoring program. The goal of this program is to enhance the protection of research subjects and improve the quality of research data. To accomplish this goal, the IRB administrative staff will send a post approval monitoring form to the principal investigator and study staff three months after the approval of a new submission.

The form includes questions about the consent process and any changes to the research that would require IRB review and approval. If, based on the responses we receive, the IRB administrative staff decides that certain study staff needs more assistance or training, the IRB/IRC staff will provide further guidance to the Investigator or study team. This program began with studies approved in September 2009.

EXECUTIVE IRB COMMITTEE

The Executive IRB Committee performs an integral function in the oversight of research at Inova Health System. The committee is charged with ensuring research policies are aligned with federal, state, and local regulations. Additionally, the committee reviews conflict of interest and research misconduct issues impacting researchers at Inova. The committee meets on a bi-monthly basis and is comprised of 14 professionals representing key areas for research.

RESEARCH QUALITY IMPROVEMENT TEAM (RQIT)

The goal of the Research Quality Improvement Team (RQIT) is to provide objective quality reviews of research studies conducted across Inova to ensure that all regulatory and clinical policies of the IRC and IRB are followed. Feedback on improvement opportunities is provided to the investigator with recommendations for implementation and to ensure studies fully comply with all appropriate regulations. Studies are randomly selected by the RQIT team and reviewed on a monthly basis. Additionally, investigators and spoke leaders may request a not-for-cause review of their studies.

The Research Quality Improvement Team (RQIT) completed eight reviews in 2009. This year the scope of reviewed studies grew to include studies taking place outside Inova Health System Fairfax Campus. Studies now come up for review by random selection of an Investigator. Studies reviewed in 2009 represented six different spokes. .

Each year, a quarterly update is provided to the IRB Executive Committee, briefly summarizing the most recent reviews and any relevant findings.

Members of RQIT consist of Susan May, MPH, CLP (IRB); Anuja Mathai, MA, JD (TTD and Contracts Office); and Rose Gorospe, RN, MSN (Research Education Office).

RESEARCH TRAINING AND EDUCATION OFFICE

The primary objective of the IRC Education Office is to provide all research programs and investigators with educational opportunities related to the conduct of research at Inova Health System. In 2009, the Education Office ended a very busy year by successfully delivering educational events and programs to researchers and those interested in learning about research throughout Inova Health System. Six research coordinators from several spokes participated in the clinical research coordinator (CRC) orientation program, which incorporates theory and practical sessions guiding coordinators on how to conduct research at Inova Health System. A clinical research staff competency tool was developed and administered to these coordinators upon completion of the program.

Quarterly education sessions were developed on the basis of feedback received from the 2nd Annual Research Training Day evaluations and administered at the Inova Fairfax Hospital campus. These sessions were well attended and offered participants the opportunity to take part in the discussions.

The 3rd Annual Research Training Day was successfully developed and delivered in conjunction with the continuing medical education (CME) Grand Rounds; Dr. Christine Grady, Acting Chief of the NIH Clinical Center's Bioethics Department, was the Key Note speaker. Over 250 attendees participated in the program including clinicians, research teams, students, residents, and other professionals.

The Education Office represented the IRC/IRB at the Annual Inova Health System Nursing Research Workshop and continued to serve on various Nursing Research boards and committees.

Administratively, the Education Office continued to develop, update, and maintain IRC standard operating procedures (SOPs), including guidance for billing research compliance, an important initiative for research in 2009. Additionally, the bi-monthly creation and dissemination of the CRC newsletter, "The Spoken News" was managed in collaboration with the IRC Database Administrator.

The Education Office team consists of Rose Gorospe, RN, MSN and Kathy Ankrah, CHEP.

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DATABASE ADMINISTRATION AND SUPPORT OFFICE

The IRC Support Office, which is responsible for the research approval process, IRC database, and maintenance of the IRC websites, focused on improving the studies listing database to allow research spokes access to their specific studies section. It offers spokes the opportunity to update the status of their studies in real time, providing better reporting.

The office processed 149 research applications in 2009, a higher volume relative to those processed in 2008, primarily due to an increased number of Executive Director Grants, and the Inova/GMU grant initiative.

The IRC webpage on Inova.net has been maintained with up-to-date information. Updates were based on feedback from the research spokes during focus group meetings. The IRC webpage on Inova.org was also revised allowing, the Center for Integrated Research (CIR) to serve as the overarching page for the site.

Administratively, the IRC Support Office developed reports as needed for senior leadership and provided oversight and maintenance of the IRC central lab.

The IRC Support Office consists of Mike Roma, MA and Terry Castro-Perez.

TECHNOLOGY TRANSFER DESK (TTD) AND CONTRACTS DESK

The primary roles of Technology Transfer Desk of the Inova Research Center are in research contract management, intellectual property management, and policy development. Additionally, TTD is involved in research quality improvement, compliance assurance, and other research process improvement initiatives.

Contracts

The desk has assisted in negotiating 13 Confidentiality Disclosure Agreements, 27 Clinical Trial Agreements, and 14 Amendments in addition to Data Use Agreements, Material Transfer Agreements, and other research related agreements.

Intellectual Property

The desk has worked with outside legal counsel and outside collaborators to file two additional patents, which brings the patent portfolio to six filings. The desk has worked with Inova legal counsel in finalizing the Intellectual Property Policy and is now developing a procedure to handle revenues generated from Intellectual Property.

Research Biospecimen Policy

The desk has developed an Inova Research Center Bio-specimen Policy that will apply to all studies taking place across Inova Health System, with a bio-specimen component.

Federal Collaborations

In conjunction with the Grants Management Office (GMO) and Corporate Accounting (CA), the desk is working on a system for better managing grants and ensuring all federal regulatory requirements are met in a timely manner. The desk has compiled a spreadsheet of all the studies that involve federal funds or collaborations. This sheet will be used by GMO and CA to ensure Inova's reporting requirements to federal entities are also met.

Academic Productivity Index (API)

Estimating academic productivity is a challenging yet increasingly important aspect of academic development. In 2009, the CIR established a committee (Zobair Younossi, MD, MPH; Michael Sheridan, ScD; Anuja Mathai, JD; and Gity Porjosh, MPH) to develop the Academic Productivity Index. Most of the work was dedicated by Anuja Mathai who not only researched the model but also worked closely with developers to establish the tool. The formula is currently being validated and will be distributed to the Inova research community for comments and eventual use in 2010.

The TTD and Contracts Office are managed by Anuja Mathai, MA, JD.

EPIDEMIOLOGY AND BIOSTATISITICS OFFICE

The activities of the IRC's Epidemiology and Biostatistics Office are primarily carried out by Michael J. Sheridan, ScD, FACE. Dr. Sheridan's major areas of effort include: 1) Design, evaluation, publication, and presentation of clinical research and quality studies; 2) Participation on Inova-wide committees governing the safety and rights of human subjects within Inova Health System; and 3) Teaching evidence-based principles and practices to Inova physicians-in-training (medical students, residents, and fellows).). In 2009, Dr. Sheridan collaborated with IHS physicians, nurses, and managers in approximately 112 clinical and quality studies across 19 departments, producing six publications in peer-reviewed journals and 12 abstracts and or presentations for national meetings of professional societies. In addition, he provided statistical expertise for the Novartis Pharmaceuticals & Inova Health Care Services Grant awarded to Kirsten Edmiston, MD.

Dr. Sheridan also served as Chair of the Inova IRB and also as a member of the Inova IRB Executive Committee.

In this capacity, he was responsible for providing ethical oversight to approximately 174 sponsored and unsponsored clinical trials involving human subjects within the Inova Health System, and in creating/revising the policies which govern all research activities within Inova Health System.

Approximately 12-15 times each month, Dr. Sheridan supervised ACGME evidence-based teaching activities for medical students, residents and fellows in the departments of medicine, obstetrics-gynecology, orthopedics, pediatrics, psychiatry, and surgery. Also, he served as Director of the CME Program for the Inova Fairfax Hospital, Department of Psychiatry, overseeing approximately 48 Category 1 AMA events. The following are the professional meetings, publications, abstracts and presentations by Dr. Sheridan, in conjunction with other investigators.

BOOKS, BOOK CHAPTERS, AND JOURNAL ARTICLES

1. Castro, M.A., Putman, C.M., Sheridan, M.J., and Cebral, J,R.: Hemodynamic patterns of anterior communicating artery aneurysms: A possible association with rupture. Am J Neuroradiol, 30:297-302, 2009.
2. Rochmis, P.G., Sheridan M.J., and Perry L. Is the NHANES III femoral neck database discordant with the total hip and trochanteric region databases? J. Clin. Densitom., 12: 224-228, 2009.
3. Malin, E., Kiernan, P.D., Sheridan, M.J., Khandhar, S.J., Fra ser, C., and Hetrick, V.: Mutlimodality treatment for esophageal malignancy: The roles of surgery and neoadjuvant therapy. Am. Surg., 75:489-497, 2009.
4. Meyr, A.J., Adams, M.L., Sheridan, M.J., and Ahalt, R.G.: Epidemiological aspects of the surgical correction of structural forefoot pathology. J. Foot Ankle Surg., 48: 543-551, 2009.
5. Meyr, A.J., Mbanuzue, Q.J., Sheridan, M.J., Kashani, A.:The laterality of the surgical correction of forefoot pathology. J. Foot Ankle Surg., 48: 5552-557, 2009.
6. Putman, C.M., Cebral, J.R., and Sheridan, M.J.: Hemodynamics and bleb formation in intracranial aneurysms. Am J Neuroradiol, 10.3174/ajnr.A1819 [Epub], 2009.

ABSTRACTS AND PRESENTATIONS TO NATIONAL MEETINGS

1. Engh, G.A., Sheridan, M.J., and Ammeen, D.J.: A New Method for Measuring Function with Knee Arthroplasty Surgery. 76th Annual AAOS Meeting, Las Vegas, Nevada, February 2009.
2. Cochran II J.W., Benson R., Mancini B.L., Lane P., Caulfield E.V., Rosecan J.V., Sheridan M.J.: Cholesterol-lowering medications and stroke outcome: Is outcome for ischemic stroke, intracranial hemorrhage and subarachnoid hemorrhage affected by cholesterol-lowering medications prior to admission to the hospital? American Stroke Association's International Stroke Conference, San Diego, CA, February 17-20, 2009.
3. Schwartz R.H., Badalyan V., Sheridan M.J.: The management of preauricular sinus. 20th Annual Meeting, Eastern Society of Pediatric Research, Philadelphia, PA, March 14-15, 2009
4. Marimon G.A., Dockery D.K., Sheridan M.J., Agarwal S.: Near-infrared spectroscopy cerebral and somatic (renal) oxygen saturation correlation to continuous venous oxygen saturation via intravenous oximetry catheter. Pediatric Academic Societies & 21st Eastern Society of Pediatric Research, Baltimore, MD, May 3, 2009
5. Cochran II J.W., Benson R.T., Lipsky R., Mancini B.L., Lane P., Sheridan M.J., Rosecan J.V.: Do cholesterol lowering medications affect outcome in ischemic stroke, intracranial hemorrhage and subarachnoid hemorrhage? American StrokeAssociation's International Stroke Conference, Washington, DC, May 4, 2009.
6. Schwartz R.H., Badalyan V., Sheridan M.J.: Diagnosis and treatment of gastro-esophageal reflux in the neonatal intensive care unit. Pediatric Academic Societies & 21st Eastern Society of Pediatric Research, Baltimore, MD, May 4, 2009.
7. Reines, H.D., Sheridan M.J., Lee L., Farmer B..: Comparison of ACS-NSQIP outcomes to Premier Quality Manager predicted outcomes: Apples and oranges? 2009 Clinical Congress of the American College of Surgeons, Chicago, IL, October 11-15, 2009.

LECTURES AND FACULTY PRESENTATIONS TO NATIONAL OR INTERNATIONAL MEETINGS

1. Society for Epidemiologic Research, June 23-26, 2009, Anaheim, CA
2. American College of Epidemiology, September 12-15, 2009, Washington, DC
3. American Public Health Association, November 7-11, 2009, Philadelphia, PA

RESEARCH FUNDS PROVIDED BY INOVA HEALTH SYSTEM

Over the past three years, Inova's senior leadership has provided two important funding mechanisms to promote and encourage original, patient-oriented research carried out by Inova investigators. The following paragraphs summarize the two mechanisms of funding.

INOVA HEALTH SYSTEM'S RESEARCH GRANTS

In 2006, Inova's senior leadership established a designated fund to provide funding for innovative and original research throughout the system. These grants include Faculty Research Grants, Seed Research Grant, and Summer Student Research Grants. Since the establishment of the funding mechanism, a total of 18 faculty grants, 26 seed grants and 13 summer student grants have been awarded.

Accordingly, in 2009, Inova awarded 27 additional research Grants to investigators in Cardiac Surgery, Pediatrics, Trauma, Orthopaedics, Women's Health, and Department of Medicine programs as well as Outcomes and Translational Research programs (14 seed grants, 8 faculty grants, and 5 student grants) for a total of $357,005.00.

GEORGE MASON UNIVERSITY-INOVA HEALTH SYSTEM LIFE SCIENCES FUND

For a decade, researchers at Inova Health System and George Mason University have been collaborating on groundbreaking research in the areas of obesity, liver disease, cancer, and heart and lung diseases. These collaborations have led to important discoveries and the development of new biomarkers as well as personalized medicine protocols. In 2009, Inova Health System provided $1 million (distributed over three years) to George Mason University to create George Mason University-Inova Health System Life Sciences Fund. This fund was established to stimulate and enhance collaborative research in the life sciences including chronic disease management, obesity, heart disease, stroke, end of life provisions, genomics, proteomics, ethical issues, and patient experience.

In July of 2009, several Inova-George Mason investigators were jointly awarded these newly established grants. The following is a summary of these grants and the award recipients:

1. Developing Procedures to Reduce Medical Anatomy and Surgery System.
   Investigators:
   Deborah Boehm-Davis –GMU
   Nicole Werner – GMU
   Maureen Burke – Inova (Risk Management)
   Award Amount: $40,000.00
2. The development of VKASS: A Virtual Knee Anatomy and Surgery System
   Investigators:
   Jim Chen – GMU
   Jihui Li – Inova – Orthopaedics
   Mark Theiss – Inova – Orthopaedics
   Craig Cheifetz – Inova – Department of Medicine
   Frank Krueger – GMU
   Award Amount: $40,000.00
3. Variation at the Oxytocin Receptor Gene Influences Responsivity of Neural Circuitry for Interpersonal Trust: Developing Molecular Mark-ers for Neuropsychiatric Disorders
   Investigators:
   Kevin McCabe – GMU
   Frank Krueger - GMU
   Robert Lipsky – Inova – Neurosciences
   Award Amount:$40,000.00
4. Antimicrobial Peptides in Idiopathic Pulmonary Fibrosis
   Investigators:
   Monique Van Hoek – GMU
   Shahzad Ahmad – Inova – Lung Transplant
   Award Amount: $40,000.00
5. Novel Methods for Sonographic Evaluation of Blunt Cervical Vascular Injuries
   Investigators:
   Siddhartha Sikdar – GMU
   Margaret Griffen – Inova – Trauma
   Anne Rizzo – Inova – Trauma
   Tayseer Al-Daghlas – Inova-Trauma
   Christopher Michetti – Inova – Trauma
   Linda Robinson – Inova – Trauma
   Award Amount: $20,000.00
6. The Perioperative Nurse's Role in Error Recovery: From Assessing Characteristics of Near Errors to Developing Interventions for Improving Quality of Surgical Care.
   Investigators:
   Tony Yang – GMU
   Linda Henry – Inova – Cardiovascular Surgery
   Award Amount: $20,000.00
7. Muscle Oxygenation and Cardiorespiratory Function in Women with SLE: Exercise Responses and Training Adaptations
   Investigators:
   Randall Keyser – GMU
   Jack Wilkenfeld – Inova – Rheumatology
   Award Amount:$10,000.00

8. Novel Risk Factors and Management Strategies for Transient Ischemic Attack (TIA) and Stroke:the Inova Fairfax Stroke Database
   Investigators:
   Panagiota Kitsantas – GMU
   Richard Benson – Inova – Neuroscience
   $10,000.00
9. The Socio-geographic Determinants of Patients with Chronic Liver Disease
   Investigators:
   Timothy Leslie – GMU
   Lisa Pawloski – GMU
   Jillian Kallman – Inova – Outcomes Research
   Yun Fang – Inova – Outcomes Research
   $10,000.00
10. Neuroanatomical Correlates and Biomarkers of Extremely Low Birth Weight Outcomes at 18 Months Corrected Age.
    Investigators:
    Jessica Lin – GMU
    Margot Ahronovich – Inova – Neonatology
    Fern Litman – Inova – Neonatology
    Ida Sue Baron – Pediatrics
    Oral Alpan – Inova – Pediatrics
    Kristine Erickson – Inova - Pediatrics
    Robin Baker – Inova - Pediatrics
    $10,000.00
11. Quantify the Contribution of Nursing to Medical Surgical Patient Care Systems at Inova Health System Hospitals.
    Investigators:
    P.J. Maddox – GMU
    Patricia Conway-Morana – Inova – Chief Nurse Executive
    $10,000.00
12. Improving Patient Care through Understanding the Nursing Work place
    Investigators:
    Margaret Mahon – GMU
    Anne Nicotera – GMU
    Xiaoquan Zhao - GMU
    Patricia Conway-Morana – Inova – Chief Nurse Executive
    $10,000.00
13. Knowledge-based Computational Models of Drug Resistance in Patients with HIV
    Investigators:
    Iosif Vaisman – GMU
    Majid Masso – GMU
    David Wheeler – Inova
    Donald Poretz – Inova – Infectious Disease
    Award Amount:$10,000.00
14. Improving Adjuvant Oral Drug Adherence among Diverse Patients with Limited Health Literacy.
    Investigator:
    Melinda Villagran – GMU
    DeWitt Webster – GMU
    Paul Clark – GMU
    Nicholas Robert – Inova – Hematology/Oncology
    $10,000.00
15. Oncology Patients' Trust in Physicians and Health Outcomes
    Investigators:
    Qiuping Zhou –GMU
    Kirsten Edmiston-Inova
    $10,000.00
16. Analysis of Pedestrian and Bicycle Motor Vehicle Crashes in the Fairfax County Region
    Investigators:
    Edmund Zolnik - GMU
    David Wong -GMU
    Anne Rizzo-Inova
    Linda Robinson-Inova
    $10,000.00

GRANTS MANAGEMENT OFFICE

Inova's Grants Management Office (GMO) pursues funding from federal, state, local, and private entities to increase financial support for existing programs and facilitate the development of new initiatives consistent with advancing Inova's mission and organizational priorities. Inova's Grants Management Office and Inova's Research Center are working collaboratively to support innovative researchers in their pursuit of funding to improve the lives of patients and bring research results from the bench to the bedside. In addition to supporting busy researchers and investigators, the GMO also coordinates and assists in developing proposals for community programs and initiatives by: identifying grant opportunities, streamlining the proposal process, providing resources/expertise to effectively prepare proposals, and providing guidance in managing grant funds and complying with grantor requirements. For 2009, GMO submitted 21 research proposals and community grants for a total of $21,824,943. Out of that: $ 8,185,365 was awarded in community grants, $5,924,595 is pending, and $ 7,714,983 was not awarded. For more information about this office and the services it provides please contact Lynn Evans-Riester, Director at Lynn.Evans-Riester@inova.org.

MEDICAL INNOVATION & TRANSFORMATION INSTITUTE (MITI):

The mission of Inova's Medical Innovation & Transformation Institute, since its establishment in 2007, has been to acquire or invent best practices in health care for the Inova process of continuous improvement. Led by Dr. Terry Sharrer, Executive Director, MITI was involved in three major projects in 2009: collaborating with the newly founded Ignite Institute for Individualized Health; exploring research, education, and business opportunities with Soochow University in Suzhou, China, and initiating a broader telemedicine program.

MĪTI received a grant from the Claude Moore Charitable Foundation to pursue several interests common to the Inova Health System and the three affiliated hospitals of Soochow University in Suzhou, about sixty miles north of Shanghai. An Inova group visited there in July, and the first of two groups coming from China arrived in Falls Church in early December. A larger delegation will follow in March 2010. At present, both sides are considering proposals for a concept called "Sinova."

Telemedicine has potential to offer more effective, efficient, and accessible healthcare, especially for elderly patients with chronic diseases. Thus, "Automated Wellness: Enabling Universal Access to Healthcare" was the title of a medical automation conference that MĪTI facilitated in early December. Wellness monitoring via wearable, implantable, or ingestible devices; step down e-care for discharged patients at home, and electronic microclinics are among the telemedicine applications MĪTI will explore for Inova.

OUTCOMES RESEARCH PROGRAM

The mission of the Outcomes Research Program (ORP) is to support Inova researchers in their efforts to develop and select appropriate outcome measures. The ORP has been established as a collaboration between Inova Health System and George Mason University. The program has completed its first year of operation in the new facility for the Center for Integrated Research and has set the course for excellence in providing support for researchers and investigators interested in measuring human performance, including real time functional activities, and patients' perceptions of their abilities and level of satisfaction.

This year ORP has broadened its range of outcomes assessment, expertise, and resources for the wider Inova research community. This is in addition to published manuscripts, a collaborative book chapter, and approved research grants, presentations at international meetings, and training the next generation of researchers. The ORP staff has also established collaborative and supportive relationships with a variety of investigators from different disciplines. These include the pediatric research group, members of Inova physical therapy and psychiatric staff, the rheumatology section, and the cardiac rehabilitation program. ORP is poised to advance research throughout the Inova Health System by using existing and future collaborations. ORP operates in a state-of-the-art functional assessment lab with equipment designed to measure aerobic capacity using gas exchange methods, ambulation patterns using in-shoe pressure measures to capture temporal and spatial data, and activities of daily living (ADL) in a simulated kitchen environment. The ability to return to the community depends upon a patient's ability to function. "Function" is the endpoint of biological organs and systems working in concert to produce purposeful activity, which is often referred to as "activities of daily living" (ADL). An individual's capacity for ADL is called "functional independence." This is a major concern for patients who are about to go home from the hospital, and those experiencing a change in mental or physical health status. Function can be improved through environmental modification and assistance with adaptive technology and personal assistants. It is important to learn about individual levels of function with appropriate research tools.

The Functional Assessment Laboratory is designed to carry out research projects that measure an individual's ability to function safely in a simulated living environment. This laboratory is designed to assess mental processing, neuromusculoskeletal, and cardiorespiratory performance of patients with chronic diseases, with each component contributing to community living. The evaluation consists of simulating kitchen activities, such as preparing food, washing dishes, loading and unloading the refrigerator. Through the use of metabolic assessment tools and blood-based biomarkers, researchers can determine the process by which these daily activities are performed, how much energy is needed, and whether a patient has the cardio-respiratory reserve to perform ADL. The measurements reliably predict the potential for independence in the community environment.

When abnormalities are observed for specific groups of patients, researchers may devise compensatory treatment plans. In addition to ADL, the Functional Assessment Laboratory studies the performance of patients with a variety of chronic diseases while they exercise by using sophisticated tools to measure cardio-respiratory system, muscle function, balance, and gait. In addition, the center uses questionnaires to assess health-related quality of life. This combined approach allows our investigators to assess several important components of function and quality of life in patients with chronic diseases.

Earlier this year the ORP supported the National Institute of Health (NIH) submission for a Stimulus Grant, coordinating efforts in bariatric surgery from Inova Fair Oaks Hospital and Inova Fairfax Hospital campuses in conjunction with George Mason University. There has been substantial administrative progress during the year.

The program has initiated an effort to develop a paperless process for capturing patient report outcomes. ORP has supported the efforts of CIR in developing a universal, electronic database for all participants in clinical research. ORP has also developed an internal network resource for all Inova research spokes to access information associated with the outcomes tools and resources to facilitate study development.

Naomi Lynn Gerber, MD, internationally renowned physician-investigator, leads the Center as the Medical Director of the Functional Assessment Laboratory. Dr. Gerber is the current director of the Center for the Study of Chronic Illness and Disability at George Mason University and brings her vast knowledge and experience as former Chief of the Rehabilitation Medicine Department at The NIH. In addition to Dr. Gerber, Jillian Kallman, MS, Program Manager of ORP provides a strong administrative base for the program, as well as years of clinical research protocol development, grant and publication submission support, education and training on the inclusion and implementation of outcomes measures in research studies within Inova Health System. Mani Srishord, RN, BSN, Administrative Director, assists and supports all aspects of the clinical operation as well as research projects. Another faculty member from George Mason University, Patrice Winter PT, MS, joined ORP in 2009. Patrice brings the experience of over thirty years as a physical therapist to the team. She is assistant faculty at George Mason University and is in the ORP lab three days per week. This team as well as other collaborators from Inova Health System and George Mason University, continue to be involved in diverse research projects.

Outcomes Research 2009 Protocols:

1. Activity and Nutritional Predictors of Response to Bariatric Surgery
2. Long Term Follow-up of Patients with Non-alcoholic Fatty Liver Disease.
3. The Impact of Age and Other Demographic Factors on the Quality of Life of Patients with Chronic Liver Disease.
4. Fatigue and Health-related Quality of Life (HRQL) Assessment in Blood Donors.
5. Pilot Study to Assess Biologic, Physiologic, Performance Measures and Self-Reports of Fatigue and Health-related Quality of Life (HRQL) in Patients with Non-alcoholic Fatty Liver Disease (NAFLD).
6. A Retrospective Assessment of Prevalence of Hepatitis B (HBV) and Hepatitis C (HCV) in the Asian Community of Northern Virginia.
7. Prevalence of Hepatitis B (HBV) and Hepatitis C (HCV) in the Asian Community of Northern Virginia.
9. Tekscan Grip and Gait Study.
10. Depression in Patients with Chronic Liver Disease.
11. Predictive Modeling of Metabolic Syndrome Complications Using Aggregated Data.
12. Is the Presence of Metabolic Syndrome Associated with Progres sion of Underlying Liver Disease
13. Nutritional Assessment in Patients with Chronic Liver Disease.
14. Socio-geographic Determinants of Patients with Chronic Liver Dis ease.
15. Resolution of Type 2 Diabetes after Bariatric Surgery.
16. Neuropsychiatric Impact of Pegylated Interferon in Hepatitis C.
17. Validation of the CLDQ-HCV in the Hepatitis C-bearing Population
18. Association of Non-Alcoholic Fatty Liver Disease (NAFLD) and Coronary Artery Disease (CAD)

Translational Research, an important constituent of the Betty and Guy Beatty Center for Integrated Research, consists of three fundamental areas: Translational Research Laboratories, Research Bio-Specimen Banking area, and Outpatient Clinical Trial area and Data Management expertise. TRI has carried out collaborative translational research with scientists from institutions such as George Mason University, Virginia Commonwealth University, and Biotechnology companies. TRI's objective is to generate innovative discoveries and pursue the development of novel biomarkers for the diagnosis and treatment of several important diseases including obesity-related liver disease and heart disease. In 2009, most of the collaborative projects for TRI were carried out with our superb collaborators from George Mason University, including Drs. Ancha Baranova, Vikas Chandhoke, Aybike Birerdinc, Lance Liotta and Chip Petricoin as well as their student and laboratory staff.

Inova's Research personnel, Noreen Hossain and Arian Afendy, enroll candidates from Inova hospitals (Inova Fairfax Hospital, Inova Heart and Vascular Institute, Inova Fair Oaks Hospital) into various TRI studies, collect and process biological specimens, and gather clinical data. In addition to biological specimens, some studies involve the collection of ultrasound imaging. TRI's current active enrollment studies include: Translational Research in Chronic Diseases, Predictors of Aggressive Disease and Responsiveness to Pegylated Interferon plus Ribavirin and the Treatment of Chronic Hepatitis C, and Association of Non-Alcoholic Fatty Liver Disease (NAFLD) and Coronary Artery Disease (CAD).

Although most activities of TRI research occur through collaboration with investigators from other institutions, many important activities are carried out at the Center for Integrated Research (CIR). Several projects are being carried out within our laboratories in this context.

In addition, TRI has the capacity to store large quantities of research specimens in -80°C freezers. The Research Bio-specimen Banking Facility can house 20 minus 80°C freezers. The freezers are kept in a temperature controlled environment with emergency generator backed electrical outlets. Additionally, to ensure the integrity of the specimens, each freezer is monitored electronically at all times for temperature fluctuations. The center is currently storing approximately 19,000 specimens from subjects enrolled in TRI studies. Additionally, the facility now houses freezers for other research spokes including Liver/Obesity Research team, the Cancer team, Cardiac Surgery team, Advanced Lung program and Neurosciences. The specimens are available for future biomarker discovery and validation.

To develop true translational research projects, the data obtained from gene expression studies must be linked to clinical and long-term outcomes data. Data obtained by using these specimens are linked to a "HIPPA compliant" clinical database (clinical, demographic, and laboratory data) which is maintained by a member of the Data Management team (Yun Fang, MS). Furthermore, the outpatient clinic of TRI is designed to provide the infrastructure for advanced clinical trials and biomarker validation protocols. TRI and all its components are managed by the Administrative Director, Manirath Srishord, RN, BSN and supported by ,Gerry Rice, who is involved in scheduling research patients, ordering supplies, and other business related issues.

TRANSLATIONAL RESEARCH LABORATORY

The Translational Research Laboratory provides several functions, including projects developed for biomarker validation and implementing personalized medicine protocols. This past year has been an exceptionally prolific year for the TRI lab. Projects have included obesity-related non-alcoholic steatohepatitis (NASH) diagnostic biomarker discovery, and an assessment of cytokines and gene expression regulation in gastric tissue of obese patients. The techniques used in this laboratory include multiplexed analysis of the soluble proteins using the Bio-Plex system, and the use of qPCR arrays for the rapid and accurate detection of gene expression.

All our projects are focused on advancing our understanding of the range of chronic liver diseases and confounding factors, including obesity, diabetes type II, and metabolic syndrome.

Most of the research projects are being conducted in collaboration with George Mason University and involve the participation and training of students from various academic levels. A majority of the experimental projects are coordinated by Dr. Aybike Birerdinc, Dr. Michael Estep, and Dr. Ancha Baranova.

David Armistead (PhD student) is working on an analysis of the miRNA profiles of the visceral adipose patients with liver fibrosis. Rohini Mehta (PhD student) is involved in gastric tissue profiling using qPCR arrays to query gastric tissue samples with the aim of discovering possible relation ships between NASH, Obesity, Type II Diabetes (T2D), and gene expression profiles.

In conjunction, undergraduate student Reem Alhussain is using the same tissue samples in a study aimed at determining the best set of housekeeping genes for the use of data normalization in qPCR studies of gastric tissue. For the same subset of patients, cytokine profiles are obtained by using the Bio-Plex system, and gastric tissue slides are stained to detect cytokine receptors. These latter studies involve students Darshan Desai (post-baccalaureate student) and Amanda Zirzow (M.S. student), respectively. Nandita Niranjan (M.S. student) is involved in the study aimed to correlate gene expression profiles of obesity-related genes with underlying polycystic ovarian syndrome (PCOS). The cytokine profiling aspect of this study using ELISA assays include esThuyTran (post-baccalaureate student).

The efficacy of various protocols for RNA and serum preservation involves the work of Beth Eom (M.S. student). We are also investigating the relationship between melanogenesis and secondary complications of obesity. This project includes the work of Massih Abawi (PhD student), Sandra Page (PhD student), and Amanda Zirzow (M.S. student).

We have published numerous abstracts for various international conferences, including the Ameri can Association for the Study of Liver Disease (AASLD), Digestive Disease Week (DDW), and the European Association for the Study of the Liver (EASL) 2009 Annual Meetings. Additionally, our team has published a large number manuscripts in various journals, including high-impact pub lications such as Hepatology, Obesity Surgery, Current Molecular Medicine, *Journal of Hepatology*, and *Journal of Viral Hepatitis*.

In 2009, we celebrated the graduation of Dr. Ganiraju Manyam and Shanna Bolden, M.S. The team looks forward to another productive and rewarding year at the TRI laboratory. Future projects in clude protocols addressing heart disease and obesity as well as other co-morbidities as we continue to research and develop diagnostic and prognostic biomarkers and provide valuable hands-on train ing opportunities for the next generation of young researchers. The following is a list of on-going projects:

1. ELISA of inflammatory cytokines involved in non-alcoholic fatty liver disease.
2. Biopanel of cytokines for non-alcoholic fatty liver disease and NASH diagnostics
3. Melanin assessment in obesity

4. Analysis of total CDT in patients with obesity-related NAFLD.
5. Detection and determination of brown adipose tissue-related genes in visceral adipose tissue
6. Determination of stable housekeeping genes for adipose tissue for the purposes of data normalization
7. Inflamatory cytokines and obesity-related panels with RNA from gastric tissue
8. Gene expression profiles in HCV-related fibrosis
9. Gene Expression Profiles in African-American with hepatitis C (HCV).
10. MicroRNA detection in visceral adipose of bariatric surgery pa tients.
11. Gastric Microbiota in post bariatric surgery patients with gastric resection
12. Gut peptide hormones and liver disease (Bio-Plex and ELISA)

DATABASE MANAGEMENT AND ANYLISIS TEAM

Yun Fang, MS (TRI) and Maria Stepanova, PhD (CLD) have worked toward the completion of management approved documentation necessary for all planned database designs, tests, implementations, upgrades and conversions These include work plans, test plans, implementation schedules, and back out recovery plans. These individuals have participated in the design and maintenance of various databases to ensure optimum performance and data integrity for all the study projects. Finally, they have ensured that tasks and projects are completed in a professional and timely manner.

Activities for 2009 are as follows:

- Designed questionnaire survey to measure PI's annual academic productivity.
- Developed electronic questionnaire for Physician flow study.
- Worked with clinical staff to develop applications identifying the right candidates for clinical trials and tracing phone log to avoid duplicated call events.
- Maintained database for Predictor study protocol.
- Introduced Oracle database server to various department and helped them understand how database applications work and how to initial ize their studies.
- Compared bariatric surgical subject's activity level with chronic liver diseases subjects.
- Provided support to a variety of studies by compiling or manipulating data.
- Collaborated with Inova Fair Oaks Hospital's Bariatric Surgery Center to perform data analysis.

Biostatistics specialists provided data analysis support for studies conducted by the research staff of the Center for Integrated Research. Biostatisticians are responsible for:

- Validating, cleaning, processing, analyzing and reporting against a wide range of biomedical datasets.
- Interfacing with the scientists to develop data analysis protocols and methods; designing and applying knowledge management as well as quality check protocols.

Development of statistical analysis methods, bioinformatics algorithms, and data mining techniques; design, implementation and annotation of programming code for data analysis; interpretation and presentation of the results of analysis of biomedical data (which, in 2009, included genomic, proteomic, outcomes, Quality of Life and cost effectiveness data, nation-wide data collections, and wet-lab experiment results).

BIO-SPECIMEN BANKING

The center's bio-specimen banking facility now houses eleven minus 80^{O}C freezers in a temperature controlled environment with backup electricity and a sophisticated electronic temperature monitoring system. Currently, over 19,000 specimens from 1800 Center for Liver Diseases' patients are stored in six freezers. Additionally, Cancer, Neurosciences, Trauma, Cardiac Surgery, and Advanced Lung research teams have acquired additional freezers that are now stored in the Bio-Specimen banking facility.

TRI OUTPATIENT CLINIC

TRI Outpatient Clinic provides innovative and cutting-edge research proto cols to help treat and manage several chronic diseases. Currently, clinical trials (Phase Ib-III) at the center consist of funded protocols. Implementation of the clinical trials is carried out by the clinical trial team, led by the Center's Research Project Manager, Fatema H. Nader, MSBM, CCRC, CCRP. Fatema received her Masters degree in Bioscience and Business Management and her Bachelor's degree in Health Science from George Mason University. She holds national certification through: the Association of Clinical Research Professionals as a Certified Clinical Research Coordinator (CCRC), and the Society of Clinical Research Associates (SoCRA).

The center customarily staffs two research coordinators and one research assistant. Heshaam Mir, MD received his Medical Degree from American University and his Bachelor's degree in Philosophy and Religion from Boston University. He has nearly four years of experience in clinical research in the area of Gastroenterology and Hepatology. Until recently, the team also included a full time coordinator, Ine-Mari Bornman, B. Soc.Sc. Ine-Mari Bornman received her (BSN) Bachelor's degree in Nursing at University of the Free State in South Africa. She possesses five years of clinical research coordinator experience, including work at a Phase I unit. Prior to joining Inova Health System, she gained experience as an in-house Clinical Research Associate. In addition, the last research member is our research assistant, Juhi Moon, MD. Juhi received her Medical Degree from Ross University and her Bachelor's degree in Biochemistry from UVA. She joined Inova Health System to gain clinical research experience before she starts her residency program next year at Allegany General Hospital in Pittsburg, PA.

RESEARCH SPOKES

Clinical and academic translational research is an integral part of Inova Fairfax Hospital Cancer Center's (IFHCC) mission to provide the highest quality care and to improve the lives of those affected by cancer. Clinical trials enable the IFHCC to provide novel therapies to patients and gain new knowledge for the future. IFHCC and its affiliated physicians are involved in a robust portfolio of collaborative intergroup clinical trials with US Oncology, Eastern Cooperative Oncology Group, ACOSOG, and CALGB. Routinely updated, these studies are available on the web at www.inova.org.

Built on the strength and diversity of our clinical volume, IFHCC physicians conduct innovative translational genomic and proteomic research in the areas of breast, lung, brain,multiple myeloma, sarcomas, and gynecologic malignancies. In 2009, IFHCC expanded its research opportunities to include additional types of cancer, increased our collaboration with new agencies and sponsors, and continued to explore future growth opportunities.

One major focus in 2009 was the important partnership with George Mason University (GMU) and the Center for Applied Proteomics and Medicine. Under the direction of Kirsten Edmiston, MD, and Lance Liotta, MD, PhD, this effort brings together the strength of clinical excellence and renowned basic science expertise to better understand the development of pre-invasive and invasive breast cancer.

Based on gracious funding from the Department of Defense and the Susan G. Komen Foundation, Inova and GMU researchers are studying the role of breast cancer stem cells and DCIS in the development of breast cancer as well as optimal ways to preserve tissues for proteomic studies. In 2009, physicians under the direction of Alexander Spira, MD and Emanuel Petricoin, PhD (GMU) opened a novel translation clinical trial using imatinib and vectibix for patients with colorectal cancer with metastatic disease with sponsorship by Novartis Pharmaceuticals.

Under the direction of Nicolas Robert, MD, IFHCC participates in the Expression Project for Oncology (expO) sponsored by the International Genomics Consortium (IGC). Additional shared research studies include participation in the Latin American Cancer Research Coalition at Georgetown University to better understand the needs of underserved patients with cancer. Other projects include collaboration with Life with Cancer in the areas of symptom and distress management under the direction of Paul Clark, PhD

Supported by the dedication of the physicians and staff, under the direction of Belinda Conte, 2010 promises to be a productive and rewarding year. The following lists the publications of the cancer research team for 2009.

BOOKS, BOOK CHAPTERS, AND JOURNAL ARTICLES

1. Espina V, Mueller C, Edmiston KH, Sciro M, Petricoin EP, Liotta LA. Tissue is alive: new technologies are needed to address the problems of protein biomarker pre-analytical variability. Accepted to Proteomics: Clinical Applications (2009)
2. Reynolds C, Barrera D, Jotte R, Spira AI, Weissman C, Boehm KA, Pritchard S, Asmar L. Phase II Trial of Nanoparticle Albumin-Bound Paclitaxel, Carboplatin, and Bevacizumab in First-line Patients with Advanced Nonsquamous Non-small Cell Lung Cancer. J Thorac Oncol. 2009 Oct 31. [Epub ahead of print]PMID: 19887966
3. Malin E, Kiernan PD, Sheridan MJ, Khandhar SJ, Fraser c, Hetrick V. Multimodality treatment for esophageal malignancy: the roles of sur gery and neoadjuvant therapy. Am Surg. 2009 Jun7;5(6):489-97.
4. Spira AI, Edmiston KH, Clinical Trials Design in the Age of Molecu lar Profiling. In Methods in Molecular Biology (edited by Espina V, Liotta LA) Humana Press, 2009 (In print)

ABSTRACTS AND PRESENTATIONS TO NATIONAL/INTERNATIONAL MEETINGS

1. Espina V, Pastore L, Adamo L, Pierobon M, Banks S, Merritt B, Zaman S, Johal J, Petricoin EF, Edmiston K, Liotta LA. Human Duc tal Carcinoma In Situ contains malignant progenitor cells.

2. Robert NJ, Dieras V, Glaspy J, Brufsky A, Bondarenko I, Lipatov O, Perez E, Yardley D, Zhou X, Phan S. RIBBON-1: Randomized, dou ble-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC). J Clin On col 27:15s, 2009 (suppl; abstr 1005)
3. Robert NJ, Discussing Costs of Care with Patients: The Community Oncology Perspective, Presentation at 2009 ASCO Annual Meeting
4. Jones SE, Collea RP, Oratz R, Paul D, Sedlacek SM, Holmes FA, Portillo RM, Crockett MW, Wang Y, Asmar L, O'Shaughnessy JA, Robert NJ. Cardiac Safety Results of a Phase II Trial of Adjuvant Docetaxel/Cyclophosphamide Plus Trastuzumab (Her TC) in HER2+ Early Stage Breast Cancer Patients presented at San Anto nio Breast Cancer Symposium, 2009.
5. Robert N, Dieras V, Glaspy J, Brufsky A, Miller KD, Miles DW, Koralewski P, Bhattacharya S, Phan S-C. Phase III Studies of Bevacizumab (B) in Com bination with Chemotherapy in Patients with HER2-Negative Metastatic Breast Cancer (MBC): Summary of Selected Adverse Events presented at San Antonio Breast Cancer Symposium, 2009.
6. Robert N, Dieras V, Glaspy J, Brufsky A, Bondarenko IN, Lipatov O, Perez E, Yardley D, Phan S-C, Bhattacharya S, O'Shaughnessy Clinical Benefit Rate and Time to Response in RIBBON-1, a Randomized, Double-Blind, Phase III Trial of Chemotherapy with or without Bevacizumab (B) for the First-Line Treatment of HER2-Negative Locally Recurrent or Metastatic Breast Cancer (MBC) presented at San Antonio Breast Cancer Symposium, 2009
7. Guarneri V, Miles D, Robert NJ, Dieras VC, Glaspy J, Smith IE, Thomssen C, Biganzoli L, Taran T, Conte P. Analysis of Bevacizu mab (Bev) Therapy, Bisphosphonate Use and Osteonecrosis of the Jaw (ONJ) in >1900 Patients Treated in Two Randomized, Controlled Trials presented at San Antonio Breast Cancer Sympos ium, 2009
8. Goss PE, Ingle JN, Martino S, Robert N, Muss H, Shepherd L, Pritchard KI, Livingston RB, Davidson N, Perez EA, Cameron D, Whelan T, Palmer M, Tu D Outcomes of Women Who Were Premeno pausal at Diagnosis of Early Stage Breast Cancer in the NCIC CTG MA17 Trial presented at San Antonio Breast Cancer Symposium, 2009.
9. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Rolski J, Chan A, Mackey J, Liu M, Pinter T, Valero V, Falkson C, Fornander T, Shiftan T, Olsen S, Buyse M, Kiskartalyi T, Landreau V, Wilson V, Press M, Crown J, Phase III Randomized Trial Comparing Doxorubicin and Cyclophosphamide Followed by Docetaxel (AC [rarr]T) with Doxorubicin and Cyclophosphamide Followed by Do cetaxel and Trastuzumab (AC[rarr]TH) with Docetaxel, Carboplatin and Trastuzumab (TCH) in Her2neu Positive Early Breast Cancer Patients: BCIRG 006 Study presented at San Antonio Breast Can cer Symposium, 2009.
10. Goss PE, Ingle JN, Martino S, Robert N, Muss H, Shepherd L, Pritchard KI, Livingston RB, Davidson N, Perez EA, Cameron D, Whelan T, Palmer M, Tu D Outcomes of Women Who Were Premenopausal at Diagnosis of Early Stage Breast Cancer in the NCIC CTG MA17 Trial presented at San Antonio Breast Cancer Symposium, 2009.
11. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Rolski J, Chan A, Mackey J, Liu M, Pinter T, Valero V, Falkson C Fornander T, Shiftan T, Olsen S, Buyse M, Kiskartalyi T, Landreau V, Wil son V, Press M, Crown J, Phase III Randomized Trial Comparing Doxorubicin and Cyclophosphamide Followed by Docetaxel (AC [rarr]T) with Doxorubicin and Cyclophos phamide Followed by Do cetaxel and Trastuzumab (AC[rarr]TH) with Docetaxel, Carboplatin and Trastuzumab (TCH) in Her2neu Positive Early Breast Cancer Patients: BCIRG 006 Study presented at San Antonio Breast Cancer Symposium,2009.
12. Hurvitz SA, Betting D, Stern HM, Quinaux E, Stinson J, Seshagiri S, Zhao Y, Buyse M, Mackey J, Robert NJ, Valero V, Crown J, Driga A, Bee V, Slamon DJ, Timmerman JM. Analysis of FcγReceptor IIA & IIIA Polymorphisms: Correlation with Outcome in Trastuzumab-Treated HER2/Neu Amplified Early and Metastatic Breast Cancer Patients presented at San Antonio Breast Cancer Symposium.

LECTURES AND FACULTY PRESENTATIONS AT NATIONAL OR INTERNATIONAL MEETINGS

1. Edmiston K, Principles of breast cancer diagnosis and treatment. Ap plication of genetics and genomics to breast cancer. BRCA1/2. Ge netic counseling. Application of gene arrays to individualized ther apy. at Bench to Bedside: Translational Cancer Research Confer ence, Catania, Italy, June 21 to June 27, 2009

2. Edmiston, K. Ethical and Regulatory Issues Surrounding Individual ized Therapy of Cancer, at Bench to Bedside: Translational Cancer Research Confer ence, Catania, Italy, June 21 to June 27, 2009
3. Wodajo FM, Bajaj GK, Multidisciplinary Treatment for Soft Tissue Sar comas: Overview and Case Presentations, Inova Oncology Grand Rounds, March 18th, 2009
4. Robert N, 2008 San Antonio Breast Cancer Update, Inova Oncology Grand Rounds, February 18th, 2009
5. Robert, N, Select Highlights from SABCS, 2008" Penn State Sympo sium, in February, 2009
6. Nguyen BL, Kanani S, Advances in Stereotactic Radiosurgery and the Program at Inova Fairfax Hospital, Department of Neuroscience Grand Rounds, February 4, 2009.

CENTER FOR LIVER DISEASES (CLD)

Inova's Center for Liver Diseases (CLD) continues to be a leader in the treatment of patients with chronic liver diseases. The center's mission is to provide patients with superb clinical care and innovative, cutting-edge research protocols. Both activities are carried out in a clinical, academic environment that involves teaching gastroenterology-hepatology fellows.

Two areas of research focus for CLD involves obesity-related fatty liver disease and hepatitis C (HCV). The spectrum of our research portfolio includes, clinical, translational, and outcomes research projects. Patients who participate in clinical research gain access to the most recent approaches in treating the two most common forms of chronic liver disease in the world.

As noted previously, within its areas of research focus, CLD carries out three types of research: Clinical Trials, Translational Research Protocols (genomics and proteomics protocols), and Health Services Research Projects, including quality of life projects.

The clinical trial part of CLD's research portfolio focuses on cutting-edge protocols for treating hepatitis C and non-alcoholic fatty liver disease (NALFD). The hepatitis C protocols are primarily phase 2-3 clinical trials of new protease, or polymerase inhibitors as well as new interferon products for HCV. These are multi-national protocols and CLD is one of the only sites in this region of the country chosen for these protocols. Furthermore, CLD is carrying out investigator-initiated protocols in NAFLD with external support but with our own IND obtained from the FDA.

The second area of research for members of the CLD is translational research. The translational research projects of CLD include gene expression, proteomics, and biomarker discovery protocols focused on obesity-related NAFLD and hepatitis C. Members of CLD are internationally recognized experts in this area of research. These pioneering protocols are performed in conjunction with colleagues from George Mason University (Drs. Ancha Baranova, Vikas Chandhoke, Lance Liotta, and Emmanuel Petricoin) as well as industry partners, such as Celera. As a result of these collaborations, CLD has secured research grants and registered five patents for biomarkers over the past year. These projects have spawned a large number of original research publications in peer-reviewed journals and presentations at international scientific meetings.

The third type of CLD research focuses on health services, primarily health-related quality of life. Again, CLD members are known internationally for their expertise in quality of life (QoL) research in liver disease. In collaboration with Inova's Outcomes Research Program, CLD maintains one of the largest QoL databases in liver disease. In collaboration with Dr. Lynn Gerber, Dr. Lisa Pawloski from GMU and Inova's Outcomes Research Program, the center is involved in functional assessment and nutritional status of patients with liver diseases.

In addition, CLD has been involved in the analysis of large databases such as NHANES III-mortality linked files to study the long term outcomes of several important liver diseases. These analysis have led to some very important data linking metabolic syndrome to mortality in patients with chronic liver disease.

In 2009, the center carried out over 34 research projects for patients with viral hepatitis and Non-alcoholic Steatohepatitis (NASH). These projects include 13 cutting-edge clinical trials, 7 translational research projects, and 14 outcomes research projects.

RESEARCH TEAM

Members of the CLD integrate their clinical practice with patient-oriented research and teaching. Manirath Srishord, RN, BSN, Administrative Director of the Center and Fatema Nader, MSBM, CCRC, Research Program Manger oversee all aspects of clinical and research personnel. In addition to Dr. Zobair Younossi, who is the principle investigator for all projects, Dr. Nila Rafiq (Research Fellow), and Brian Lam, PA-C (Physician Assistant), are sub-investigators for these protocols.

In addition to the Clinical Trial Team, the Translational Research projects of the CLD is supported by a part-time Research Assistant, Arian Afendy,

BS, who has been working with CLD for the past three years. She is responsible for several important translational research projects for specimen collection, data collection, and data entry, and actively participates in presenting findings at national and international meetings.

Hepatitis C Clinical Research:

The year 2009 was marked by several important increases in clinical research activity. Hepatitis C continues to present a serious health challenge that affects 170 million people worldwide, including 4 million in the United States and 8 million in Europe and Japan. Because a sustained viral response is less than 50% in hepatitis C patients infected with genotype 1 when they are treated with the current standard of care (pegylated IFN-α plus ribavirin), new and more effective treatments are much needed. Our hepatitis C protocols are primarily Phase II-III clinical trials of new protease or polymerase inhibitors and new interferon agents for treating hepatitis C. These are multi-national protocols and CLD is one of the only sites in this region of the county chosen to participate. To date, a total of 39 subjects have been enrolled in the various hepatitis C protocols as described below:

1. A phase 3 Study of 2 Dose Regimens of Telaprevier in Combination with Peginterferon Alfa-2a (Pegasys®) and Ribavirin (Copegus®) in Treatment- Naïve Subjects with Genotype 1 Chronic Hepatitis C.
2. A Phase 3 Study of 2 Dose Regimens of Telaprevier in Combination with Peginterferon Alfa-2a (Pegasys®) and Ribavirin (Copegus®) in Genotype 1 Hepatitis C Subjects who have not Achieved Sustained Viral Response with a prior Course of Interferon Based Therapy.
3. A Phase 2 study of Telaprevir (VX-950) in Combination with Pefinterferon Alfa-2a (Pegasys®) and Ribavirin (Copegus®) in Subjects with Genotype 1 Hepatitis C who have not Achieved Sustained Viral Response with a Prior Course of Interferon-Based Therapy.
4. A Phase 2, Randomized, Double-blind, Placeob-controlled Study to Evaluate the Safety and Efficacy of Filibuvir plus Pegylated Interferon Alpha-2a and Ribavirin in Treatment Naïve, HCV Genotype 1 infected Subjects.
5. A Phase 2b, Double-blind, Randomized, Parallel-group, Placeob-controlled Study to Evaluate the Safety, Tolerability and Efficacy of GS-9450 in Adults with Chronic Hepatits C Virus Infection.
6. A Phase 2, Randomized, Double-Blind, Placebo-controlled, Ascending Multiple Dose Trial of the Safety, Efficacy, and Phrmacokinetics of ANA598 Administered with Pegylated Interferon and Ribavirin in Treatment- Naïve Genotype 1 Patients with Chronic Hepatitis C Infection.
7. Phase 2B, PartiallyBlinded, Radomized Study in Treatment- Naïve Subject with HCV Genotype 1 to compare the Efficacy, Safety, and Tolerability of three doses of LoctEron™ Plus Ribavirin given Bi-weekly in Comparison with PEG-Intron™ plus Ribavirin Given weekly.
8. EXTEND: a 3-year, Virology follow-up Study in Subjects Previously Treated with Telaprevir in Select Clinical Studies.
9. Hepatitis C Trial: A phase II randomized, multicenter, open-label study of HCV therapeutic Vaccine (TG4040) in combination with pegylated interferon alfa-2a and ribavirin versus pefylated interferon alfa-2a and ribavirin in treatment- naïve patients with chronic genotype 1 hepatitis C.
10. Hepatitis C Trial: Controlled clinical study of a VX-222 and Telaprevier based regimen in combination with Peginterferon alfa-2a or Ribavirin in treatment- naïve subjects with genotype 1 chronic hepatitis C.

Non-alcoholic Steatohepatitis (NASH) Clinical Research:

Currently, no effective therapies are available for treating non-alcoholic steatohepatitis. and because the pathogenesis of NASH is unknown, thereapeutic strategies are chiefly empirical. Over the past 15 years, Dr. Younossi and his team have been considered international leaders in the study of this important liver disease.

The center is currently carrying out a large number of translational research projects (please see TRI), outcomes research projects (please see Outcomes Research Program), and clinical research in non-alcoholic fatty liver disease. In terms of clinical trials in NAFLD, the center carries out an investigator initiated protocol in NASH with external industry support but with an IND our center obtained from the FDA. The study teams involved in conducting this investigator-initiated trial includes the clinical research team, data management team, regulatory affairs, outcomes research as well as translational research team. Currently, a total of 38 subjects have been enrolled in the NASH protocols as described below:

1. Investigator Initiated Trail: Open Label Clinical Trial of High Dose URSO in Severely Obese Persons with Non-alcoholic Steatohepatitis (NASH Undergoing Bariatric Surgery.
2. Investigator Initiated Trial: Open Label Clinical Trial of High Dose URSO in Combination with Vitamin E in Severely Obese Persons with Non-alcoholic Steatohepatitis (NASH) Undergoing Bariatric Surgery.

PAGE 26 CLD CONTINUED

Clinical Research Personnel

Members of the CLD integrated their clinical practice in Hepatology with patient-oriented research and teaching. Inova's Center for Liver Diseases clinical research department is staffed by Manirath Srishord, MSN, RN, the Administrative Director of the center; Fatema Nader, MSBM, CCRC, the Research Program Manager; a Research Project Manager, two Research Coordinators, and a Research Assistant. Student researchers have also contributed to various research activities at the center.

The following are publications and presentations by the researchers of the Center for Liver Diseases for 2009:

BOOKS, BOOK CHAPTER, AND JOURNAL ARTICLES

1. Z Younossi, J Capeau (Co-Editors). Metabolic Complications from Hepatitis C. Liver International (Supplement): Volume 29, Supplement 2; 2009
2. A Baranova, A Birerdinc, M Estep, ZM Younossi. Pathogenesis of obesity-related chronic liver diseases as the study case for the systems biology. *Textbook of Systems Biology for Signaling Networks* (Sangdun Choi, Editor). 2009
3. Z Younossi. Epidemiology and Clinical Presentation of Non Alcoholic Fatty Liver Disease. *Proceeding of 8th International Meeting on Therapy in Liver* Disease 2010 (In Press).
4. J Kallman, Z Younossi. Quality of Life After Liver Transplantation for Hepatitis C. *Hepatitis C And Liver Transplantation Textbook* (Sandeep Mukherjee, MBBCh, Editor), 2010 (In press)
5. Nila Rafiq, and Zobair M. Younossi. Hepatic Changes of Obesity and the Effects of Weight Loss. *Handbook of Obesity Surgery.* Current Concepts and Therapy of Morbid Obesity and Related Diseases. Editors: Mervyn Deitel, Michel Gagner, John B. Dixon, Atul K. Madan, Jacques Himpens (In Press 2010)
6. M Randhawa, T Huff, JC Valencia, ZM Younossi, V Chandhoke, VJ. Hearing, A Baranova. Evidence for the Ectopic Synthesis of Melanin in Human Adipose Tissue. FASEB J. 2009 Mar;23 (3):835-43.
7. N Rafiq, CH Bai, Y Fang, M Srishord, A McCullough, T Gramlich, ZM Younossi. Long-Term Follow-Up of Patients with Non- Alcoholic Fatty Liver. Clinical Gastro and Hepatology 2009; 7(2):234-8
8. Z Younossi, A McCullough. Metabolic Syndrome, Non-Alcoholic Fatty Liver Disease and Hepatitis C Virus: Impact on Disease Progression and Treatment Response. Liver Int 2009 Mar; 29 Suppl 2:3-12.
9. B Lam, Z Younossi. Treatment of Non-Alcoholic Fatty Liver Disease. Annals of Hepatology 2009; 8 (1): Supplement: S51-S59
10. Kallman JB, Arsalla A, Park V, Dhungel S, Bhatia P, Haddad D, Wheeler A, Younossi ZM. Screening for Non-alcoholic Fatty Liver Disease (NAFLD), Hepatitis B (HBV) and Hepatitis C (HCV: A Survey of Community-based Physicians. Aliment Pharmacol Ther.2009 May 1;29(9):1019-24.
11. N Rafiq, Z Younossi. Evaluation and Management of Non-Alcoholic Fatty Liver Disease. Clinics in Liver Disease 2009; 13:249–266
12. JM Estep, A Baranova, N Hossain, H Elariny, K Ankrah, A Afendy, V Chandhoke, ZM. Younossi. Expression of Cytokine Signaling Genes in Non-Alcoholic Steatohepatitis and Hepatic Fibrosis. Obes Surg. 2009 May;19 (5):617-24.
13. N Hossain, A Afendy, M Stepanova, F Nader, M Srishord, Z Goodman, Z Younossi. Independent Predictors of Fibrosis in Patients with Non-Alcoholic Fatty Liver Disease. Clin Gastroenterol Hepatol. Nov 2009;7(11):1224-9
14. ZM. Younossi, A Afendy, M Stepanova, N Hossain, I Younossi, K Ankrah, T Gramlich, A Baranova. Gene Expression Profile Associated with Superimposed Non-Alcoholic Fatty Liver Disease in Patients with Chronic Hepatitis C. Liver Int. 2009 Jun 3. [Epub ahead of print]
15. J Ong, M Stepanova, ZM Younossi. Outcomes of patients with Non-Alcoholic Fatty Liver Disease. J of Hepatology 2009 May 27. [Epub ahead of print]
16. B Lam, ZM Younossi. Treatment options for Non-Alcoholic Fatty Liver Disease. Therapeutic Advances in Gastroenterology 2010 (In Press).
17. M Stepanova, N Houssain, A Afendy, ZD. Goodman, A Baranova, ZM Younossi. Hepatic Gene Expression of Caucasian and African-American Patients with Non-Alcoholic Fatty Liver Disease. Obesity Surgery 2010 (In Press).
18. JP Ong, ZM Younossi. Non-Alcoholic Fatty Liver Disease after Liver Transplantation: A Case of Nurture and Nature. Am J of Gastroenterology 2010 (In Press).
19. M Stepanova, R Aquino, A Alsheddi, R Gupta, Y Fang, ZM Younossi. Clinical Predictors of Fibrosis in Patients with Chronic Liver Disease. Aliment Pharmacol Ther 2010 (In Press).
20. Z Younossi, A Baranova, M Stepanova, V Calvert, A Afendy, Z Goodman, L Liotta, E Petricoin. Proteomics Biomarkers Predicting Non-Alcoholic Steatoheaptitis and Fibrosis. (In press 2010)
21. J Kallman, A Wheeler, HK Alathari, Y Fang, M Stepanova, H Elrainy, ZM Younossi. Association of Components of Metabolic Syn

drome with Depression and Anxiety in Patients Undergoing Weight Reduction Surgery. Submitted 2010
22. M Estep, D Armistead, N Hossain, H Elarainy, Z Goodman, A Baranova, ZM Younossi. Differential Expression of miRNAs in the Visceral Adipose of Patients with Non-Alcoholic Fatty Liver Disease. In Press (2010)
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25. Afendy, J Kallman, M Stepanova, Z Younoszai, R Aquino, G Bian chi, G Marchesini, ZM Younossi. Predictors of Health-Related Quality Of Life (HRQL) In Patients with Chronic Liver Disease. Ali ment Pharmacol Ther 2009;30(5):469-76
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28. Z Younosssi. Mechanisms of Viral Eradication and Early Treat ment in Hepatitis C: Implications for Therapy Clinical Update. AGA/Medscape Clinical Update; Published December 2009.
29. ZM. Younossi, A Baranova, A Afendy, R Collantes, A Bakshi, M Stepanova, G Manyam, C Santini, C Sigua, J Chan, A Iverson, SY Chang. Gene Expression Biomarkers Predicting Sustained Vi rologic Response in Patients with Chronic Hepatitis C Treated with Pegylated Interferon Alfa and Ribavirin. Hepatology 2009 Mar; 49(3):763-74.
30. J Capeau, S Gharakhanian, Z Younossi. Metabolic Abnormali ties in Chronic Hepatitis C. Introduction Liver Int. 2009 Mar; 29 Suppl 2:1-2.
31. M Estep, Z Younossi. Hepatitis C and Metabolic Syndrome. Ex pert Review of Endocrinology and Metabolism 2010 (In Press)
32. J Kallman, S Tran, A Arsalla, D Haddad, M Stepanova, Y Fang, VJ. Wrobel, M Srishord, ZM. Younossi. Vietnamese Community Screening for Hepatitis B (HBV) and Hepatitis C. J of Viral Hepatitis 2010 (In Press)
33. A Baranova, M H. Jarrar, M Stepanova, A Johnson, N Rafiq, T Gramlich, V. Chandhoke, ZM. Younossi. Association of Serum Adipocytokines with Hepatic Steatosis and Fibrosis in Patients with Chronic Hepatitis C. (In press 2010)
34. G Aragon, Z Younossi. Evaluation of Asymptomatic Elevation of Liver Enzymes. Cleveland Clinic J of Med 2009 (In Press).
35. M Estep, A Birerdinc, ZM Younossi. Biomarkers, the Pillars of Molecular Diagnostics and Personalized Medicine Revolution. Current Molecular Medicine (In Press 2010))
36. JM Estep, G Grant, L O'Reilly, J Piper, J Jonsson, J Assmann, V Chandhoke, Z Younossi. Gene Expression Profile Associated with Hepatic Stellate Cells: Implications for Hepatic Fibrosis. Dig Dis Sci. 2010; 55:496–504

ABSTRACTS AND PRESENTATIONS TO NATIONAL/ INTERNATIONAL MEETINGS

1. Nila Rafiq, Maria Stepanova, Brian Lam, and Zobair M. Younossi. Type 2 Diabetes, Obesity And Hypertension Are As sociated With Mortality In Hepatitis C Patients. European Asso ciation for the Study of Liver, Copenhagen, Denmark 2009 (Oral Presentation)
2. Zobair M. Younossi, Ancha Baranova, Maria Stepanova, Valerie S. Calvert, Arian Afendy, Zachary Goodman, Lance Liotta, Emanuel Petricoin. Proteomics Biomarkers Predicting Histologic Non-Alcoholic Steatoheaptitis And Fibrosis. European Associa tion for the Study of Liver, Copenhagen, Denmark 2009
3. Ancha Baranova, Nila Rafiq, Ishmeet Kaur, Noreen Hossain, Manpreet Randhawa, Vikas Chandhoke, Zobair M. Younossi. Differences of Adipocytokine Between Non-Alcoholic Fatty Liver Disease And Coronary Artery Disease. European Association for the Study of Liver, Copenhagen, Denmark 2009
4. Stepanova, Maria, Rafiq, Nila; Mir, Heshaam M.; Bornman, Ine-Mari; Younossi, Zobair M. Mortality and Liver Related Mortality in Patients with Chronic Liver Disease: Association with Compo nents of Metabolic Syndrome (MS) Digestive Disease Week, Chicago, Illinois, 2009 (Oral Presentation).
5. Hossain, Noreen; Afendy, Arian; Stepanova, Maria; Rafiq, Nila; Nader, Fatema; Srishord, Manirath K.; Goodman, Zachary D.; Younossi, Zobair M. Independent Predictors of Fibrosis in a

Large Cohort of Patients with Non-Alcoholic Fatty Liver Dis ease. Digestive Disease Week, Chicago, Illinois, 2009.
6. Estep, Michael; Birerdinc, Aybike; Wheeler, Angela M.; Page, Sandy; Stepanova, Maria; Baranova, Ancha; Alathari, Husam K.; Younossi, Zobair M. Carbohydrate-Deficient Transferrin in Pa tients with Fatty Liver Disease. Submitted to Obesity Meeting 2009.
7. Garone, Michael; Kallman, Jillian; Aquino, Ruben D. ; Fang, Yun; Lee, Phuong; Elariny, Hazem A.; Younossi, Zobair M. Activity Level in Patients Undergoing Bariatric Surgery. Digestive Dis ease Week, Chicago, Illinois, 2009.
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9. D Armistead, M J. Estep, M Stepanova, G Manyam, N Rafiq, H Elariny, A Baranova, ZD. Goodman, ZM. Younossi Differential Expression of miRNA in Patients with Non-alcoholic Steatohepa titis. American Association For Study Of Liver Disease 2009, Boston MA
10. M Estep, ABirerdinc, AWheeler, S Page, A Baranova, HAlathari, Z Younossi. Carbohydrate-Deficient Transferrin in Patients with Fatty Liver Disease Undergoing Bariatric Surgery. The Obesity Society's Annual Scientific Meeting, Washington DC, Oct 2009
11. ZM. Younossi, N Rafiq, S Page, M Stepanova, N Hossain, A Birerdinc, ZD. Goodman, A Baranova. A Novel Serum-based Biomarker Panel for Non-alcoholic Steatohepatitis (NASH) and NASH-related Fibrosis. American Association For Study Of Liver Disease 2009, Boston MA
12. Noreen Hossain, Maria Stepanova, Arian Afendy, Fatema Nader, Nila Rafiq, Zachary D. Goodman, Zobair M. Younossi. Non- a l c o holic Steatohepatis (NASH) in Patients with Polycystic Ovarian Syndrome (PCOS). American Association for Study Of Liver Disease 2009, Boston MA.
13. Sandra Page, Nila Rafiq, Maria Stepanova, Arian Afendy, Aybike Birerdinc, Zachary D. Goodman, Ancha Baranova, Zobair M. Younossi. Comparison of Different Biomarkers for Patients with Non-alcoholic Steatohepatitis. American Association for Study of Liver Disease 2009, Boston MA.
14. J M Estep, D. Armistead, M Stepanova, N. Hossain, H. Elariny, A Baranova, Z Goodman, V Chandhoke, Z Younossi. Serum Cyto kines and the Expression of miRNAs in the Visceral Adipose of Patients with Non-alcoholic Fatty Liver Disease. European Asso ciation for the Study of Liver Disease Meeting 2010. Oral Presen tation
15. M Stepanova, D Limongi, A Afendy, M Pierobon, I Younossi, T Gramlich, L Liotta, E Petricoin, Z Younossi. Protein Pathway Bio markers Signature Associated with Superimposed Non-Alcoholic Steatohepatitis (NASH) and Advanced Fibrosis in Patients with Chronic Hepatitis C. European Association for the Study of Liver Disease, 45th Annual Meeting 2010, Vienna, Austria.
16. R Mehta, A Birerdinc, N Hossain, A Moazez, V Chandhoke, A Baranova, ZM Younossi. Profiling and Validation of Reference Genes in the Visceral Adipose Tissue (VAT). Digestive Disease Week, Annual Meeting 2010, New Orleans, Louisiana
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18. D Desai, M Estep, A Birerdinc, H Mir, A Baranova, V Chandhoke, Z Younossi. Markers of Insulin Resistance During HCV Treatment: A Relationship to Sustained Virologic Response (SVR). Digestive Disease Week, Annual Meeting 2010, New Orleans, Louisiana
19. M Estep, M Abawi, S Bolden, M Stepanova, N Hossain, Z Good man, V Chandhoke, A Baranova, Z Younossi. Serum Obestatin Concentrations in Non-alcoholic Fatty Liver Disease (NAFLD) with Fibrosis. Digestive Disease Week, Annual Meeting 2010, New Or leans, Louisiana (Submitted).
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21. J Kallman, A Afendy, M Stepanova, Maria, Younoszai, Zahra, Aquino, Ruben D, Bianchi, Giampaolo, Marchesini, Giulio, Younossi, Zobair M. Health-relate Quality of Life (HRQL) in Pa tients with Chronic Liver Diseases. Digestive Disease Week, Chicdago, Illinois, 2009.
22. Weinstein, Lynn Gerber, Jillian Kallman, Yun Fang, Patrice Winter, Juhi Moon, and Zobair Younossi. Relationship between Chronic

Sleep Restriction and Health-Related Quality of Life. American Psychosomatic Society 68th Annual Scientific Meeting, March 10 - 14, 2010, Porland,OR

23. J Moon, J Kallman, Z Younoszai, Zahra, P Winter, Y Fang, L Ger ber, ZM Younossi. Validation of Chronic Liver Disease-HCV Ver sion (CLDQ-HCV) with Fatigue Severity Scale. Digestive Disease Week, Annual Meeting 2010, New Orleans, Louisiana
24. NL Gerber, J Kallman, I Kaur, Y Fang, ZM Younossi. Demo graphic, diagnostic and disease characteristics of patients with chronic liver disease correlates with physical activity. ISPRM Is tanbul, Turkey, 2009
25. Nila Rafiq, Maria Stepanova, Heshaam M. Mir, Ine-Mari Born man, Brian Lam, Manirath Srishord, Zobair M. Younossi. Diabe tes Related Mortality in Patients with Chronic Liver Disease. American Association for Study of Liver Disease 2009, Boston MA (Oral Presentation).
26. Jillian B. Kallman, Sang V. Tran, Aimal Arsalla, Dmitri Haddad, Maria Stepanova, Fang Yun, Valerie Wrobel, Manirath Srishord, Zobair M. Younossi. Screening for Hepatitis B (HBV) and Hepati tis C (HCV) in a Vietnamese Community of Northern Virginia. American Association For Study Of Liver Disease 2009, Boston MA.
27. C Gennings, R Agrawal, Y Fang, C Bach, B Lam, ZM Younossi. Stratification and Prediction of Outcomes of Bariatric Surgery Pa tients using the Relative Wellness Index (RWI). Digestive Disease Week, Annual Meeting 2010, New Orleans, Louisiana
28. E. Lawitz, Z.M. Younossi, M. Shiffman, S. Gordon, R. Ghalib, W. Long, A. Muir, J. McHutchison. Randomized Trial Comparing Systemic And Local Reactions To Controlled-Release Interferon Alpha2b And Pegylated-Interferon Alpha2b In Hepatitis C Pa tients Who Failed Prior Treatment. European Association for the Study of Liver, Copenhagen, Denmark 2009
29. A Birerdinc, A Afendy, M Stepanova, I Younossi, G Manyam, A Baranova, ZM. Younossi. Functional Pathway Analysis of Genes Associated with Response to Treatment in Chronic Hepatitis C (CH-C). American Association for the Study of Liver Dis eases' (AASLD) The Henry M. and Lillian Stratton Basic Research Single Topic Conference 2009, Atlanta, GA
30. E. Lawitz, Z.M. Younossi,P. Mehri, A. Rigney, Z. Krastev,K. Tchernev, D. Takov, W. Long. Randomized, Partially-Blinded 72-Week Phase 2b Study (Select-2) Comparing Controlled-Release Interferon Alpha2b and Pegylated-Interferon Alpha2b in Treatment-Naïve Genotype 1 Hepatitis C: 12 Week Results. European Association for the Study of Liver Disease Meeting 45th Annual Meeting 2010, Vienna, Austria.
31. Z. Younossi, D Limongi, M Stepanova, M Pierobon, A Afendy, L. Liotta, E. Petricoin. Protein Pathway Biomarkers Predicting Sustained Virologic Response (SVR) to Pegylated Interferon (PEG-IFN) and Ribavirin (RBV) in Patients with Chronic Hepatitis C (CH-C). European Association for the Study of Liver Disease, 45th Annual Meeting 2010, Vienna, Austria.
32. G Manyam, I Younossi, T Gramlich, A Baranova, Z Younossi, A Birerdinc, M Stepanova, A Afendy. Up-regulation of Matrix Met alloproteinase 9 (MMP-9) and Interleukin-8 (IL-8) inAfrican-American Patients with Chronic Hepatitis C. Digestive Disease Week, Annual Meeting 201 0, New Orleans, Louisiana
33. D Limongi, M Stepanova, A Afendy, M Pierobon , R Agrawal, L Liotta, E Petricoin, ZM Younossi. Protein Pathway Biomarkers Predicting Sustained Virologic Response (SVR) to Pegylated Interferon (PEG-IFN) and Ribavirin (RBV) in Treatment-Naive Genotype 1 Patients with Chronic Hepatitis C. Digestive Disease Week, Annual Meeting 2010, New Orleans, Louisiana. Oral Presentation, Plenary Session
34. D Desai, M Estep, A Birerdinc, H Mir, A Baranova, V Chandhoke, ZM Younossi. Markers of Insulin Resistance in During HCV Treatment: A Relationship to Sustained Virologic Response (SVR) Digestive Disease Week, Annual Meeting 201 0, New Orleans, Louisiana
35. A Birerdinc, M Stepanova, A Afendy, G Manyam, I Younossi, T Gramlich, A Baranova, ZM Younossi. Up-Regulation of Matrix Metalloproteinase 9 (MMP-9) and Interleukin-8 (IL-8) in African-Americans Patients with Chronic Hepatitis C. Digestive Disease Week, Annual Meeting 201 0, New Orleans, Louisiana (Submitted)
36. J Moon, J Kallman, P Winter, LR. Pawloski, ZM Younossi. Meas urement of Physical Activity in Patients Infected With Chronic Hepatitis C Virus (HCV). 138th APHA Annual Meeting (November 6-10, 2010), Denver, CO. (Submitted)
37. W.A. Long, D. Takov, K. Tchernev, I. Kotzev, A. Rigney, Z. Krastev, S. Stoynov, R. Balabanska, E. Lawitz, Z. Younossi, R. Ghalib, E. Zuckerman, R. Safadi, R. Tur-Kaspa, N. Assy, Y. Lurie.

Q2week Controlled-Release-Interferon-Alpha2b+Ribavrin Reduces Flu-Like Symptoms >50% And Provides Equivalent Efficacy In Comparison To Weekly Pegylated-Interferon Alpha2b+Ribavirin In Treatment-Naïve-Genotype-1-Chronic-hepatitis-C: Results From Empower, A Randomized-Open-Label-12-

38. J Moon, J Kallman, P Winter, LR. Pawloski, ZM Younossi. Measurement of Physical Activity in Patients Infected With Chronic Hepatitis C Virus (HCV). 138th APHA Annual Meeting (November 6-10, 2010), Denver, CO. (Submitted)
39. W.A. Long, D. Takov, K. Tchernev, I. Kotzev, A. Rigney, Z. Krastev, S. Stoynov, R. Balabanska, E. Lawitz, Z. Younossi, R. Ghalib, E. Zuckerman, R. Safadi, R. Tur-Kaspa, N. Assy, Y. Lurie. Q2week Controlled-Release-Interferon-Alpha2b+Ribavrin Reduces Flu-Like Symptoms >50% And Provides Equivalent Efficacy In Comparison To Weekly Pegylated-Interferon-Alpha2b+Ribavirin In Treatment-Naïve- Genotype-1-Chronic- Hepatitis-C: Results From Empower, A Randomized-Open-Label-12-
40. Week-Comparison In 133 Patients. European Association for the Study of Liver Disease Meeting 45th Annual Meeting 2010 Vienna, Austria. Late Breaker (Submitted)
41. SS Lee, EJ Heathcote, W Sievert, H Trinh, K Kaita, ZM Younossi, J George, M Shiffman, P Marcellin, J Sorbel, J Anderson, E Mon dou, J Quinn, Franck Rousseau. Tenofovir Disoproxil Fumarate (TDF) Versus Adefovir Dipivoxil (ADV) In Asians With HBeAg-Positive And HBeAb-Negative Chronic Hepatitis B Participating In Studies 102 And 103. The 13th International Symposium on Viral Hepatitis and Liver Disease (ISVHLD) 2009
42. Rubin Aquino, Maria Stepanova, Abdulellah Alsheddi, Ravindra Gupta, Fang Yun, Zobair M. Younossi. Independent Predictors of Fibrosis in Patients with Chronic Liver Disease. American Associa tion For Study Of Liver Disease 2009, Boston MA
43. S Lee, Jacobs, Z Younossi, E Mandoux. Three Years Efficacy and Safety of Tenofovir Disoproxil Fumarate (TDF) in Asians with HBeAg-positive and HBeAg-negative Chronic Hepatitis B, Preliminary Analysis. American Association for Study of Liver Disease 2009, Boston MA.
44. Z. Younossi, M. Stepanova. Independent Predictors Of Hepatocelluar Carcinoma (Hcc)-Related Mortality And Non-HCC Liver-Related Mortality: A Population Based Study. European Association for the Study of Liver Disease Meeting 45th Annual Meeting 2010, Vienna, Austria. Late Breaker (Submitted)

LECTURES AND FACULTY PRESENTATIONS TO NATIONAL OR INTERNATIONAL MEETINGS

1. Non-alcoholic Fatty Liver Research. Mount Sinai School of Medicine Liver Research Seminar. January 2009
2. Natural history and clinical evaluation of NAFLD and NASH. "8th International Meeting on Therapy in Liver Diseases", Barcelona, Spain, September 2009
3. Update in the Treatment for Non-alcoholic Fatty Liver Disease (NAFLD). General Hepatology Update Course, American Association for the Study of Liver Disease, Boston, MA, November 2009
4. Diagnosing NAFLD/NASH: Who to Screen and How to Confirm the Diagnosis? UEGW/WCOG GASTRO 2009, London, United Kingdom, November 2009
5. Non-alcoholic Fatty Liver Disease. Carolinas Medical Center-CME Liver Course, Charlotte, NC, December 2009.
6. Hepatic Encephalopathy-CME, Chronic Liver Disease Foundation, Las Vegas, NV January 2010
7. NAFLD and NASH. Scripps Clinic 25th Annual Treatment in Chronic Liver Disease March 2010
8. Controversy: Results from PIVENS Trial (IR is not Important). Scripps Clinic 25th Annual Treatment in Chronic Liver Disease, March 2010
9. NASH: Noninvasive Markers – Emerging Alternatives to Biopsy: Measuring steatosis, fibrosis and cell death. Symposium: What's New and Hot in Clinical Hepatology. Digestive Disease Week 2010, New Orleans, LA, May 2010
10. Non-Alcoholic Fatty Liver Disease: When should I biopsy? How should I treat? American College of Gastroenterology Annual Meeting, Post Graduate Course 2010, San Antonio, Texas, October 2010.
11. The Role of Liver Biopsy in the Future Management of NAFLD. Early Breakfast Session, American College of Gastroenterology Annual Meeting, San Antonio, Texas, October 2010.
12. Quality of Life in Chronic Liver Disease, Chairperson for the Session. UEGW/WCOG GASTRO 2009, London, United Kingdom, November 2009
13. Hepatitis B and Hepatitis C Content Development Meeting. Chronic Liver Disease Foundation, Dallas, TX 2009

14. The Past, Present, and Future of Hepatitis C: A Discussion With the Experts. AGA Institute and Medscape, Chicago 2009
15. Hepatitis C and Metabolic Syndrome. CMETV, Chronic Liver Disease Foundation, Chicago 2009
16. STAT-C Therapy for Chronic Hepatitis C Round Table (Chair), New York, NY November 2009
17. Hepatic Encephalopathy CME Meeting. Chronic Liver Disease Foundation Dallas 2009
18. Management of Overt Hepatic Encephalopathy CME Tele conference, Chronic Liver Disease Foundation 2009.
19. Hepatic Encephalopathy Content Development Meeting. Chronic Liver Disease Foundation, Chicago, IL 2009.

The Gynecologic Oncology Research program is a new program currently under development. The program currently involves several investigators including Dr. Annette Bicher, Dr. John Elkas, Dr. Hans Krebs, Dr. Ruchi Garg, Sheila Whitt, RN, BSN and Angela Alonge, BS.

The goals of the program include:

1. Support translational research at the National Cancer Institute with tissue collection studies.
2. Participate in National Cooperative group studies in ovarian, endometrial, cervical and vulvar cancer when available.
3. Participate in Phase II/III studies primarily in ovarian cancers to aid in evaluation of efficacy of novel therapeutic agents in the treatment of advanced/recurrent disease.

The program is currently involved in several GOG projects and industry-sponsored and NCI sponsored protocols. Within the next year the research team plans to grow their research portfolio and their academic productivity.

The research team did not provide a list of publications and presentations.

The Inova Advanced Lung Disease and Transplant Program is dedicated to the care of patients with many forms of advanced lung disease, including conditions such as chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis (IPF), pulmonary hypertension (PH), cystic fibrosis, and sarcoidosis.

The research program has numerous facets including pharmaceutical drug trials of medications for IPF, PH, and lung transplantation, and active clinical and research collaboration with the NIH through the intramurally funded NIH-Inova Advanced Lung Disease Program. Genomics research into IPF is conducted through a collaboration with George Mason University. In addition, original Inova investigator initiated projects account for most of the publications emanating from the Program. The Program has also collaborated with esteemed research institutions such as the Cleveland Clinics, Mayo Clinic, UCLA, Johns Hopkins, The University of Florida, the University of Pittsburgh, and Vanderbilt University. In 2009, the program's research resulted in thirteen original research papers published or submitted to the peer-reviewed literature, and 22 presentations at or submitted to international meetings. The research program owes its success to the dedication of our research coordinators, a close collaborative environment, and most importantly the patients themselves, who continue to empower and enable the research by their willingness to participate in the clinical trials.

BOOKS, BOOK CHAPTERS, AND JOURNAL ARTICLES

1. Shlobin OA, Nathan SD. Interstitial lung disease and pulmonary hy pertension. (edited by Robert Baughman, MD and Ronald du Bois, MD)
2. Barnett CF, Bonura EJ, Nathan SD, Ahmad S, Shlobin O, Osei K, Zaiman AL, Hassoun PM, Moller DR, Barnett SD, Girgis RE. The Treatment of sarcoidosis associated pulmonary hypertension: a two center experience. Chest 2009;135:1455-1461
3. El-Chemaly S, Malide D, Zudaire E, Ikeda Y, Weinberg B, Pacheco-Rodriguez G, Rosas I, MacDonald SD, Wu H, Nathan SD, Cutitta F, McCoy JP, Gochuico BR, Moss J. Abnormal Lymphangiogenesis in Idiopathic Pulmonary Fibrosis: Insights into Cellular and Molecular Mechanisms.PNAS2009http://www/pnas.org/content/early/2009/02/20/0813368106.abstract
4. King CS, Khandhar S, Burton N, Shlobin OA, Ahmad S, Barnett SD, Nathan SD. Native Lung Complications In Single Lung Transplant Recipients And the Role of Pneumonectomy. J Heart Lung Trans plant 2009;28:851-6
5. Nathan SD, Shlobin OA, Reese E, Ahmad S, Fregoso M, Athale C, Barnett SD. The Prognostic Value of the Six-minute Walk Test in Pa tients with Bronchiolitis Obliterans Syndrome. Respiratory Medicine 2009;103:1816-21.
6. Sunde JS, Chetty-John S, Shlobin OA, Boice C, Rose GS. Epstein-Barr Virus Associated Uterine Leiomyosarcoma in an Adult Lung Transplant Patient. Accepted to Obstetrics and Gynecology.

ABSTRACTS AND PRESENTATIONS TO NATIONAL/ INTERNATIONAL MEETINGS

1. Shlobin OA, Edwards E, Nathan SD. Waiting Times and Mortality for IPF Patients Listed for Bilateral or Single Lung Transplantation. J Heart Lung Transplant 2009;28:S168.
2. S Ahmad, OA Shlobin, SD Barnett, EA Lefrak, ME Schmidt, N Bur ton, SD Nathan. Cytomegaloviral Shedding in Bronchoalveolar Lav age (BAL) in Lung Transplant Recipients: Comparison of Oral Val ganciclovir to IV and Oral Ganciclovir Based Prophylactic Regimens. Am J Respir Crit Care Med 2009;179:A4609
3. S Kilaru, OA Shlobin, S Ahmad, SD Barnett, SD Nathan. Combined

Pulmonary Hypertension (PH) and Interstitial Lung Disease in Con nective Tissue Disorders: The Role of PH Therapy. Am J Respir Crit Care Med 2009;179:A4928

4. Nathan SD, Ferrer G, Shlobin OA. Regional Perfusion and Ventila tion in Patients with Idiopathic Pulmonary Fibrosis Complicated by Pulmonary Hypertension. Am J Respir Crit Care Med 2009;179:A4055
5. King CS, Khandhar S, Burton N, Shlobin OA, Ahmad S, Fregoso M, Athale C, Barnett SD, Nathan SD. Native Lung Complications In Single Lung Transplant Recipients And The Role of Pneumonec tomy. Am J Respir Crit Care Med 2009;179:A4610
6. Saadla H, Shlobin OA, Barnett SD, Battle E, Brenner R, Ahmad S, Nathan SD. The Six Minute Walk Test Comparison to a Stair Climbing Test. Am J Respir Crit Care Med 2009;179:A4408
7. Chhina M, Nathan SD, Emblom-Callahan MC, Shlobin OA, Ahmad S, Reese ES, Brenner R, Grant GM. Proliferative profile of IPF pul monary fibroblasts. Am J Respir Crit Care Med 2009;179:A3480
8. Basavaraj A, Barnett SD, Kiernan J, Shlobin OA, Ahmad S, Nathan SD. Prevalence of Unsuspected Coronary Artery Disease in P atients with Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med (Award Winner) 2009;179:A4052
9. Woodrow JP, Shlobin OA, Barnett SD, Nathan SD. Prognostic Impli cation of Spirometric Patterns in Patients with Bronchiolitis Obliter ans Syndrome Complicating Lung Transplantation. Am J Respir Crit Care Med 2009;179:A2539
10. Woodrow JP, Shlobin OA, Ahmad S, Nathan SD. Prognosis Associ ated with Bronchiolitis Obliterans Syndrome Compared to Chronic Allograft Dysfunction Following Lung Transplantation. Am J Respir Crit Care Med 2009;179:A2538
11. Mosburg J, Shlobin O, Barnett S, Nathan SD. Prevalence and Im pact of Anemia and Polycythemia in Patients with Idiopathic Pulmo nary Fibrosis Am J Respir Crit Care Med 2009;179:A4051
12. SD Nathan, OA Shlobin, J Kiernan, N Weir, A Basavaraj, S Ahmad, MJ Sheridan, J Earls. High Resolution Computed Axial Tomography of the Chest for the Detection of Coronary Artery Disease in patients with Idiopathic Pulmonary Fibrosis. Accepted to Chest 2009. Nomi nated as semifinalist for Alfred Soffer Research award
13. Woodrow J, Nathan SD, Shlobin OA. Idiopathic Nonspecific Intersti tial Pneumonitis Treated With Triple Immunosuppression. Presented at Chest 2009
14. M Chhina, MC Emblom-Callahan, GM Grant, SD Nathan. Beta-actin protein over-expression in IPF pulmonary myofibroblasts *in vivo*. Best basic research poster (Award Winner) Washington DC Thoracic Society meeting, April 2009.

LECTURES AND FACULTY PRESENTATIONS TO NATIONAL/ INTERNATIONAL MEETINGS

1. Pulmonary Hypertension:Who to treat and when? Medical Grand Rounds, George Washington Hospital, March 5th, 2009
2. Pulmonary Hypertension: Who to treat, when and then…. Cardiol ogy Grand Rounds. Mary Washington Hospital, Fredericks burg, VA March 19th 2009
3. Lung transplantation: Who, when and then… Virginia Association of Cardiac and Pulmonary Rehabilitation conference, March 21st University of Mary Washington, Fredericksburg, VA
4. Pulmonary Hypertension: Who to treat and when? Winchester Medi cal Center Grand Rounds. April 1st 2009
5. Current Concepts in the Management of Advanced Lung Disease. University of Wisconsin Annual Conference: Key Note Speaker, April 10th, 2009.
6. Approach to the Treatment of PAH. International Society for Aero solized Medicine. May 14th 2009. Monterey, CA.
7. Lung Transplantation for PAH. Diagnosis and Therapy of PAH: State of the Art. Postgraduate course ATS San Diego May 14th 2009.
8. Pre-transplant Management of Advanced Lung Disease. Lung Transplantation: State of the Art. Postgraduate course ATS San Diego May 14th 2009.
9. Approach to the Treatment of PAH. International Society for Aero solized Medicine. May 14th 2009. Monterey, CA.
10. Lung Transplantation for PAH. Diagnosis and Therapy of PAH: State of the Art. Postgraduate course ATS San Diego May 14th 2009.
11. Pre-transplant Management of Advanced Lung Disease. Lung Transplantation: State of the Art. Postgraduate course ATS San Diego May 14th 2009.
12. Conservative Management or Vasoactive Therapy for PH Associ ated with Parenchymal Lung Disease. Controversies in PH Manage ment. Postgraduate course ATS San Diego May 14th 2009.
13. Pulmonary Hypertension in Patients with Interstitial Lung Diseases, Interstitial Pneumonia and Sarcoidosis. Meet the Professor session. ATS May 17th 2009. San Diego

14. The treatment of Mycetoma. Session on Clinical Problems in Sarcoi dosis. ATS May 18th 2009. San Diego
15. Session Chair: Controversies in the Management of IPF. ATS meet ing May 20th, 2009. San Diego
16. Pulmonary Hypertension in IPF: Seek and Treat? Session on Con troversies in the Management of IPF. ATS meeting May 20th, 2009. San Diego
17. Pulmonary Hypertension: Who to treat and when? Howard Univer sity Medical Grand Rounds June 2nd 2009
18. Pulmonary Hypertension in COPD and IPF. Annual Yale Pulmonary Hypertension conference, Hartford, CT June 4th, 2009
19. Pulmonary Hypertension:Medical and Surgical Treatments. Harley Hinton Lecture Series, Southside Regional Medical Center, Peters burg, VA
20. COPD:Before and beyond bronchodilators. Medical Grand Rounds, Beth Israel Hospital, Newark, NJ, June 18th 2009.
21. Pulmonary Hypertension in Interstitial Lung Disease. Mid-West Pul monary Vascular conference Kansas City, Kansas October 3rd 2009
22. Pulmonary Hypertension complicating advanced Pulmonary Fibro sis: To treat or not? Rochester University Pulmonary Grand Rounds. October 7th, 2009
23. The Management of Pulmonary Hypertension. Advanced Lung Dis ease Post-graduate course. American College of Chest Physicians November 1st 2009. San Diego
24. IPF and Pulmonary Hypertension. St. Vincent's Hospital, Dublin, Ireland November 26th 2009
25. Sarcoidosis and Lung Transplantation. The Mater Hospital, Dublin, Ireland November 27th 2009
26. Pulmonary Arterial Hypertension and Lung Transplantation. Annual Tufts Pulmonary Hypertension Conference, Boston MA, Dec 4th, 2009.
27. Interstitial Lung Disease in Connective Tissue Disorders. Update in Pulmonary and Critical Care conference. Cleveland Clinics, Branton, FL. Dec 5th, 2009.

INOVA HEART AND VASCULAR INSTITUTE (IHVI)

Inova Heart and Vascular Institute's cardiology research encompasses several areas of expertise including Interventional Cardiology, Electrophysiology, Heart Failure, and Heart Transplant. In 2009, patients were enrolled in studies across all disciplines. There were approximately seventeen active protocols and registries enrolling patients with others in the patient follow-up stage.

ADVANCE D HEART FAILURE STUDIES

- Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS)
- Prospective Evaluation of Elastic Restraint to Lessen the Effects of Heart Failure (PEERLESS HF) Trial
- Reducing Decompensation Events Utilizing Intracardiac Pressures in Patients with Chronic HF - Chronicle ICD Implantable Cardio verter Defibrillator (REDUCE HF)
- Evaluation of the VentrAssist Left Ventricular Assist Device as a Bridge to Cardiac Transplantation-Pivotal Trial
- Evaluation of the VentrAssist™ Left Ventricular Assist Device for the Treatment of Advanced Heart Failure - Destination Therapy
- Double-blinded Placebo-Controlled, Multicenter Acute Study of Clini cal Effectiveness of Nesiritide in Subjects with Decompensated Heart Failure (ASCEND HF)
- Evaluation of the HeartWare® Left Ventricular Assist Device (LVAD) System for the Treatment of Advanced Heart Failure

INTERVENTIONAL/DIAGNOSTIC CARDIOLOGY

- Coronary Stent Graft Use in Coronary Aneurysm, HDE Number H000001
- A Clinical Evaluation of the Medtronic Endeavor® Resolute Zo tarolimus-Eluting Coronary Stent System in the Treatment of De Novo Lesions in Native Coronary Arteries with a Reference Vessel Diameter of 2.25 mm to 4.2 mm.

PEDIATRIC/ADULT CONGENITAL INTERVENTIONAL CARDIOLOGY

- Patent Foramen Ovale closure with the AMPLATZER PFO OC CLUDER in Patients with Recurrent Cryprogenic Stroke due to pre sumed paradoxical embolism through a Patent Foramen Ovale who have failed conventional drug therapy (PFO ACCESS Registry)
- Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using the AMPLATZER PFO Occluder compared to Medical Management (PREMIUM)

ELECTROPHYSIOLOGY

- Optimum Lead Insulation Material Registry
- Response of Cardiac Resynchronization Therapy Optimization with V-V Timing in Heart Failure Patients (Response HF)
- Continued Access Protocol for the Evaluation of Catheter Cryoabla tion in the Treatment of Paroxysmal Atrial Fibrillation
  MAGELLAN: A Randomized Controlled Trial of Radiofrequency Ab lation for the Treatment of Paroxysmal Atrial Fibrillation Using the Bard High Density Mesh Ablation System
- SMARTDELAY determined AV Optimization: A comparison to Other AV Delay Methods Used in Cardiac Resynchronization (SMART-AV).

CARDIOLOGY-CV SURGERY

- Use of the Accumetrics VerifyNow P2Y12 Platelet Function As say to Determine Readiness for Cardiac Surgery after Receiv ing a P2Y12 ADP binding site inhibitor During Coronary Cathe terization and/or Percutaneous Coronary Intervention

BOOKS, BOOK CHAPTERS AND JOURNAL ARTICLES

1. Rajesh Kabra, Chirag M. Sandesara, Christopher J. Berry. "Cardiology". In MA Graber and JK Graber (Eds.), Family Practice

2. Chirag M Sandesara, MD, and Richard E Kerber, MD. "Indications and Techniques of Electrical Defibrillation and Cardioversion". In Hurst, Schlant, Sonnenblick, and Wenger (Eds), The Heart. 12th ed. (187-198). New York: McGraw Hill, 2009.
3. Gopinathannair R, Sandesara CM, Olshansky B. Not so innocent bystander(s). Europace. 2009 Jun 18. [Epub ahead of print]
4. Kabra R, Gopinathannair R, Sandesara C, Messinger C, Olshansky B. The dual role of implantable loop recorder in patients with potentially arrhythmic symptoms: a retrospective single-center study. Pacing Clin Electrophysiology. 2009 Jul;32 (7):908-12.

LECTURES AT LOCAL MEETINGS

1. Christopher May, MD. Cardiac Allograft Rejection. Transplant Grand Rounds. Inova Heart and Vascular Institute, Fairfax, VA
2. Chirag Sandesara, MD. Managing Cardiac Arrhythmias. Inova Heart and Vascular Institute Smart Heart Meeting. Inova Heart and Vascular Institute, Fairfax, VA
3. Chirag Sandesara, MD. Cardiac Sarcoidosis. From Granulo mas to Sudden Death and Everything in Between. Cardiology Grand Grounds, Prince William Hospital, Manassas, VA
4. Chirag Sandesara, MD. A Healthy Heart: How to Take Care of It. Mini Medical School, Fauquier Hospital, Warrenton, VA
5. Chirag Sandesara, MD. Predictors of Sudden Cardiac Death. Virginia Cardiovascular Foundation CME, Prince William Hospital, Manassas, VA

INOVA HEART AND VASCULAR INSTITUTE (IHVI) CARDIAC SURGERY RESEARCH

The IHVI Cardiac Surgery Research Program is a leader in clinical and basic research for cardiac conditions such as atrial fibrillation and valve disease, and also provides training for future clinicians. The program was established to enhance cardiac surgery research at the Inova Heart and Vascular Institute (IHVI) and was designed to create a multi-disciplinary team focused on conducting research in three core areas: clinical, health-related quality of life and outcomes, and bench science. Research on atrial fibrillation and valve disease are particular areas of interest within these core areas. We also are involved in clinical trials involving cardiothoracic surgery, which are carried out by Rx Trials on a contractual basis with IHVI -IFHC.

Our team consists of the following individuals: Niv Ad, MD (Director) Shalin P. Desai, MD (Research Fellow) , Linda L. Henry, PhD, RN (Research Investigator), Sari D. Holmes, PhD (Manager, Epidemiology & Biostatistics), Sharon L. Hunt, MBA (Senior Database Administrator), Lisa M. Martin, PhD (Research Administrator), Lori E. Stone, BS (Research Project Associate), Chidima T. Martin, BS (Research Project Associate), Cshantara L. Woolfolk, BS (Research Project Associate) and Linda S Halpin, RN, MSN (Clinical Practice Specialist).

Academically, this past year was quite productive with a large number of abstract submissions, poster presentations, oral presentations, faculty presentations, and published journal articles. We also received one Inova Executive Director Research Grant for Summer Students and submitted three National Institutes of Health and one National Science Foundation grant applications.

BOOKS, BOOK CHAPTERS AND JOURNAL ARTICLES

1. Ad N, Henry L, Hunt S, Barnett S, Stone L. The Cox-Maze III proce dure success rate: comparison by electrocardiogram, 24-hour holter monitoring and long-term monitoring. Annals of Thoracic Surgery. 2009 Jul;88(1):101-5.
2. Henry LL, Ad N, Martin LM, Hunt SL, Crippen P. A Quality Improve ment Project to Optimize Patient Outcomes Following the Maze Pro cedure. Journal of Nursing Care Quality, 2009;24(2):160-5.
3. Ad N, Barnett SD, Haan CK, O'Brien SM, Milford-Beland S, Speir AM. Does Preoperative Atrial Fibrillation Increase the Risk for Mor tality and Morbidity after Coronary Artery Bypass Grafting? JTCVS, 2009 Apr;137(4):901-6.
4. Barnett SD, Ad N. Surgery for Aortic and Mitral Valve Disease in the United State: A Trend of Change in Surgical Practice Between 1998 and 2005. JTCVS, 2009 Jun;137(6):1422-9.
5. Khandar S, Nitzschke S, Ad N. Left atrioesophageal fistula following catheter ablation for atrial fibrillation: Off bypass, primary repair us ingan extrapericardial approach. J Thorac CardioVasc Surg. 2009 Mar 116. (Epub ahead of print).
6. Tran HA, Barnett SD, Hunt SL, Chon A, Ad N. The effect of Previ ous Coronary Artery Stenting on Short and Intermediate- term Out come After Surgical Revascularization in Patients with Diabetes Mellitus. J Thorac Cardiovasc Surg. 2009 Aug;138(2):276-7.
7. Barnett SD, Martin LM, Halpin LS, Ad N. Impact of Body Mass Index on Clinical Outcome and Health-Related Quality of Life Following Open Heart Surgery. J Nurs Care Qual. 2009 Aug 26 (Epub ahead of print). 2010 Jan-Mar;25(1):65-72
8. Martin LM, Barnett SD, Henry LL, Ad N. An Examination of Health-Related Quality of Life Following Open Heart Surgery: A Meta-Analysis. JTCVS, 2009, In Press.
9. Martin LM, Barnett SD, Henry LL, Lemus EL, Stone LE, Hunt SL, Ad N. Gender Disparities in Health-Related Quality of Life Outcomes Af ter Surgery. Circulation: Cardiovascular Quality and Outcomes, 2009, In Press

10. Martin LM, Barnett SD, Henry LL, Lemus EL, Stone LE, Hunt SL, Ad N. Gender Disparities in Health-Related Quality of Life Outcomes After Surgery. Circulation: Cardiovascular Quality and Outcomes, 2009, In Press.
11. Ad N, Henry LL, Halpin L, Hunt SL, Barnett SD, Crippen P, de Bullet S, Lamberti J. The Use of Spirometry Testing prior to Cardiac Surgery may impact the Society of Thoracic Surgeons risk prediction Score: A prospective study in a Cohort of Patients at high risk for chronic lung disease. JTCVS, 2009, In Press. (Epub ahead of print).
12. Speir AM, Kasirajan V, Barnett SD, Fonner E Jr. Additive costs of postoperative complications for isolated coronary artery bypass grafting patients in Virginia. Ann Thorac Surg. 2009 Jul;88(1):40-5; discussion 45-6.
13. Ad N, Henry LL, Hunt SL. Minimally Invasive Maze III Procedure Performed Without Aortic Clamping. Innovations, 2009, In Press.
14. Bogot NR, Shaham D, Berman PM, Elami A, Sosna J, Ad N. The Effect of the Cryosurgical Cox-Maze Procedure on Pulmonary Veins Diameter and Left Atrial Size: Computed Tomography Angiographic Assessment. Innovations. 2009 Jul/Aug; 4:209-216.
15. Ad N. The Surgical Treatment for Atrial Fibrillation: Should the Maze be Modified? Innovations. 2009 Sep/Oct;4:238-239.
16. Ad N. The Quest to Identify Predictors for Success and Failure folloing the Cox-Maze procedure for the treatment of atrial fibrillation. J Thorac Cardiovasc Surg, 2009 In Press
17. Halpin L, Henry LL, Dunning E, Hunt S, Barnett S, Ad N. Comparison of Blood Glucose Management Strategies to Achieve Control Following Cardiac Surgery (Computerized Versus Paper). AACN Clinical Issues, 2009, In Press.
18. Martin C, Henry L, Martin L, Ad N. Steps for Successful Implementation of Proteomic Research in the Operating Room. Association of peri-Operative Nurses Journal (AORN), 2009, In Press.

ABSTRACTS AND PRESENTATIONS TO NATIONAL/INTERNATIONAL MEETINGS

1. Ad N, Henry LL, Hunt SL. The Success Rate Following Maze III Procedure: A Comparison between EKG, 24 Hours Holter and Long Term Monitoring.The Society of Thoracic Surgeons 45th Annual Meeting, San Francisco, California, January 2009.
2. Tran HA, Barnett SD, Hunt SL, Ad N. The Society of Thoracic Surgery Risk Model Accurately Predicts Survival and Perioperative Complications Following High-Risk Aortic Valve Replacement. The American College of Surgeons 58th Annual Meeting, Orlando, Florida, March 2009.
3. Henry LL, Martin LM, Hunt SL, Barnett SD, Halpin L, Ad N. The Association of Survival and Patient Disposition Following Coronary Artery Bypass Surgery. 9th Scientific Forum on Quality Care and Outcomes Research in Cardiovascular Disease and Stroke, American Heart Association, Annual Meeting, Washington, DC, April 2009.
4. Hunt SL, Henry LL, Martin LM, Ad N. Describing the Success of the Maze Surgical Procedure: More than Just a Simple Statistic. 9th Scientific Forum on Quality Care and Outcomes Research in Cardiovascular Disease and Stroke, American Heart Association, Annual Meeting, Washington, DC, April 2009.
5. Martin LM, Barnett SD, Henry LL, Lemus EL, Stone LE, Hunt SL, Ad N. Gender Disparities in Health-Related Quality of Life Outcomes After Surgery. 9th Scientific Forum on Quality Care and Outcomes Research in Cardiovascular Disease and Stroke, American Heart Association, Annual Meeting, Washington, DC, April 2009.
6. Martin LM, Henry LL, Stone LE, Tran HA, Ad N. The Cardiac Surgery Experience: Patients' Perspectives. 9th Scientific Forum on Quality Care and Outcomes Research in Cardiovascular Disease and Stroke, American Heart Association, Annual Meeting, Washington, DC, April 2009.
7. Martin LM, Barnett SD, Henry LL, Ad N. Health-Related Quality of Life Following Open-Heart Surgery: A Meta-Analysis. 9th Scientific Forum on Quality Care and Outcomes Research in Cardiovascular Disease and Stroke, American Heart Association, Annual Meeting, Washington, DC, April 2009.
8. Anderson J, Henry LL, Hunt SL, Halpin L, Martin LM, White J, Ad N, Speir A. Use of the Bispectral Index Monitor (BIS) when Extubating Cardiac Surgery Patients. National Teaching Institute, Critical Care Nurses, Annual Meeting, New Orleans, May 2009.
9. Ad N, Hunt SL, Henry LL, Martin LM, Stone LE. Success of Surgical Ablation in Patients with Long Standing Persistent Atrial Fibrillation (AF). 30th Annual Scientific Sessions, Heart Rhythm Society, Boston, Massachusetts, May 2009.
10. Ad N, Henry LL, Hunt SL. The Success Rate Following Maze III Procedure: A Comparison Between EKG, 24 Hour Holter and Long Term Monitoring. 30th Annual Scientific Sessions, Heart Rhythm Society, Boston, Massachusetts, May 2009.

11. Goudarzi M, Ross M, Zhou W, Van Meter A, Petricoin E, Liotta L, Martin L, Martin C, Ad N. Discovery of Mitochondrial Protein Biomarkers of Atrial Fibrillation Using Unique Human Tissue Samples. 57th American Society for Mass Spectrometry (ASMS) Conference on Mass Spectrometry, Philadelphia, PA, May-June 2009
12. Hunt S, Henry L, Martin L, Ad N. Managing Atrial Fibrillation Data Post Maze Procedure: Registry Design, Cost and Effectiveness Academy Health, 2009 Annual Research Meeting, Chicago, IL, June 2009.
13. Massimiano P, Tran H, Henry L, Hunt S, Barnett S, Sheikh W, Martin C, Ad N. The Evolution of Minimally Invasive Mitral Valve Repair: From Heartport Through Da Vinci to Fibrillation Without Cross-Clamping. Society for Heart Valve Disease, Berlin, Germany, June 2009.
14. Tran H, Barnett S, Aljijani A, Ad N. One-year Survival Following Isolated Aortic Valve Replacement: A Comparison of 4 Risk Prediction Models. Society for Heart Valve Disease, Berlin,Germany, June 2009.
15. Ad N, Henry LL, Hunt S, Stone L. The Implementation of a Comprehensive Clinical Protocol Improves Long Term Success Following Surgical Treatment of Atrial Fibrillation. Western Thoracic Surgical Association, Banff, Canada, June 2009.
16. Hunt S, Henry, LL, Martin LM, Ad N. Atrial Fibrillation Module for Patients Undergoing Cox-Maze Procedure: How to Manage New Hospital Data Elements and Follow-up Beyond Thirty Days. The Society of Thoracic Surgeons- Advances in Quality & Outcomes: A Data Manager's Meeting, San Diego, CA, September 2009.
17. Martin LM, Henry LL, Stone LE, Martin CT, Ad N. The Lived Recovery Experiences of Women Cardiac Surgery Patients. International Society for Quality of Life Research 16th Annual Conference, New Orleans, LA, October 2009.
18. Henry LL, Martin LM, Stone LE, Ad N. Women's lived experiences of recovery after cardiac surgery. American Public Health Association 137th Annual Meeting, Philadelphia, PA, November 2009.
19. Goudarzi M, Ross M, Zhou W, Van Meter A, Deng J, Liotta L, Petricoin E, Martin L, Martin C, Ad N. Discovery of mitochondrial protein biomarkers of atrial fibrillation using unique human tissue samples. American Association for Clinical Chemistry: Translating Novel Biomarkers to Clinical Practice: Roleand Opportunities for the Clinical Laboratory, Bethesda, MD,November 2009.

LECTURES AND FACULTY PRESENTATIONS TO NATIONAL OR INTERNATIONAL MEETINGS:

1. Speir AM, Kasirajan V, Fonner E. Addiditive Costs of Post-Operative Complications in Virginia. The Society of Thoracic Surgeons 45th Annual Meeting, San Francisco, California, January 2009.
2. Ad N. A Minimally Invasive Full Maze Lesion Set for Atrial Fibrillation: Technique and Results.
3. Boston Atrial Fibrillation Symposium. Boston, Massachusetts, January 2009.
4. Ad N, Henry LL, Hunt SL. Minimally Invasive Maze III Procedure Performed Without Aortic Clamping. ISMICS, San Francisco, California, June 2009.
5. Henry LL, Martin LM, Halpin L, White J. Nurses' Perception of the Extubation Process for the Stable Cardiac Surgery Patient. Sigma Theta Tau International Honor Society of Nursing, Cancun, Mexico, July 2009.
6. Ad N, Henry LL, Hunt S, Stone L. The Implementation of a Comprehensive Clinical Protocol Improves Long Term Success Following Surgical Treatment of Atrial Fibrillation. Western Thoracic Surgical Association, Banff, Canada, June 2009.
7. Henry L, Hunt S, Ad N. Stable Sinus Rhythm Following the Maze Procedure With Valve Surgery Results in Significant Improvement in Health Related Quality of Life. Society for Heart Valve Disease, Berlin, Germany, June 2009.
8. Henry L, Martin L, Halpin L, White J. Nurses' Perception of the Extubation Process for the Stable Cardiac Surgery Patient. 20th International Nursing Research Congress, Vancouver, BC, Canada, July 2009.
9. Tran H, Opraseuss J, Dean L, Ad N. Acute Kidney Injury Network Classification Improves Prediction of Perioperative Complications and Long-Term Survival After CABG; Comparative Study of STS Definitions. American College of Surgeons 95th Annual Clinical Congress, Chicago, IL, October 2009.
10. Henry LL, Ad N, Lamberti JP, Halpin L, Hunt S, Barnett SD, Speir AM, Crippen P. The significance of Preoperative Spirometry in Accurately Stratifying the Predicted Risk for Adverse Outcomes in Cardiac Surgery Patients. American College of Chest Physicians (CHEST) 2009, San Diego, CA, November 2009

11. Tran HA, Barnett SD, Hunt S, Martin L, Ad N. Preoperative Risk Factors for Acute Kidney Injury Following Cardiac Catheterization and CABG. American College of Chest Physicians (CHEST) 2009, San Diego, CA, November 2009.
12. Henry LL, Tran HA, Freighling T, Durrani SA, Wish M, Bell M, Del Negro A, Ad N. Outcome of Surgical and Catheter Ablation to Treat Atrial Fibrillation. Southern Thoracic Surgical Association Annual Meeting, Marco Island, FL, November 2009.
13. Martin LM, Henry LL, Stone LE, Martin CT, Barnett SD, Hunt SL, Ad N. Health-Related Quality of Life of those Aged 65 or Older after Open-Heart Surgery. American Public Health Association 137th Annual Meeting, Philadelphia, PA, November 2009.
14. Ad N, Henry LL, Hunt S. Cardiac Interventions Prior to Surgical Ablation for Atrial Fibrillation- Do Not Negatively Affect Outcomes. American Heart Association Scientific Sessions 2009, Orlando, FL, November 2009.
15. Niv Ad – Lecture – Surgical Ablation: The Real Results. STS/AATS Technical Conference, January 2009.
16. Dr. Niv Ad - Post-Graduate Course, Surgical Treatment for AF: Are We Ready for Prime-Time? AATS, San Francisco, California, January 2009.
17. Dr. Niv Ad – Moderator, Speaker, Panelist - Cardiovascular Research Institute Annual Meeting & Workshop with the FDA – Washington, District of Columbia – March 2009.
18. Dr. Niv Ad - Lecture – Minimally Invasive Maze III Procedure without Aortic Cross Clamping Using Cryoablation Technology. Advanced Cardiac Techniques in Surgery, May 2009.
19. Dr. Niv Ad – Moderator – Atrial Fibrillation symposium. Advanced Cardiac Techniques in Surgery, May 2009.
20. Dr. Niv Ad – Post-Graduate Course, ISMICS, San Francisco, California, June 2009.
21. Dr. Niv Ad – Moderator, ISMICS, San Francisco, California, June 2009.
22. Dr. Niv Ad – Invited Speaker – ISMICS, San Francisco, CA – June 2009. Cox-Maze Procedure,Minimally Invasive Cryomaze III Procedure Performed without Aortic Clamping
23. Dr. Niv Ad – The Impact of a Collaborative Approach between Cardiology and Cardiac Surgery on the Atrial Fibrillation (AF) Surgery Program – Grand Round – University of Ottawa, Canada, June 2009.
24. The Impact of a Collaborative Approach between Cardiology and Cardiac Surgery on the Atrial Fibrillation (AF) Surgery Program – Grand Round – University of Ottawa, Canada, June 2009.
25. Minimally Invasive Cryoblation Maze Procedure – Grand Round – Coswig, Germany, July 2009.
26. Minimally Invasive Cryoblation Maze Procedure - Visiting Surgeon and Grand Round – Luebeck, Germany, July 2009.
27. Minimally Invasive Cryoblation Maze Procedure – Grand Round – Badoyenhausen, Germany, July 2009.
28. The Maze Procedure: A dialogue concerning definition and goals – Faculty Speaker for Grand Rounds for Cardiothoracic Surgery – Albany Medical College, Department of Surgery, Albany, New York, September 2009.
29. The Surgical Treatment of Atrial Fibrillation: Minimally Invasive Cryo-Maze III Without Aortic Cross Clamping – Faculty Speaker for ATS Medical. European Association for Cardio-Thoracic Surgery 23rd Annual Meeting, Vienna, Austria, October 2009.
30. Cryosurgery for the Treatment of Cardiac Arrhythmia – Frontiers in Cryoblation Symposium – Faculty Speaker. European Association for Cardio-Thoracic Surgery 23rd Annual Meeting, Vienna, Austria, October 2009.

In 2009, there were a number of industry sponsored research protocols carried out by members of Interventional radiology. The following is a summary of these protocols:

1. **Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL)**

- Prospective, multicenter, unblinded, two arm, randomized trial designed to test the hypothesis that medical therapy with stenting of hemodynamically significant (angiographically documented) renal artery stenosis in patients with systolic hypertension reduces the incidence of cardiovascular and renal events com pared with medical therapy alone.
- Primary Endpoint: Event-free survival from cardiovascular and renal adverse events defined as a composite of cardiovascular or renal death, stroke, MI, hospitalization for CHF, progressive renal insufficiency, or need for permanent renal replacement therapy.
- Enrollment goal 1080 subjects with 200 sites internationally.
- Follow subjects for up to 5 years, closely monitoring for blood pressure control and management of other risk factors.

A subgroup of 400 patients will undergo renal artery Duplex ultrasound at baseline, 1 year and study termination.

2. **CRUX Biomedical Evaluation of the Crux Inferior Vena Cava Filter System – ("Retrieve")**

- This is an open label, non-randomized, prospective, multicenter study.
- Primary Efficacy Objective: To describe the clinical utility of the Crux IVCF by the following criteria: Absence of a recurrent PE and IVC thrombosis related to the Crux IVCF
- Primary Safety Objective: To estimate the proportion of patients who experience device/procedure related complications associated with the Crux IVCF. 104 patients considered to be at risk for PE are expected to be enrolled in this study. It is anticipated that approximately 30 patients will undergo retrieval of the implanted filter.

3. **SIR-Spheres Registry**

- Nationwide registry for all subjects undergoing SIR-Spheres procedure
- The purpose of the Registry is to build a Phase IV (i.e., post-marketing) database of patient demographics, primary and secondary diagnoses, treatment details, complications and patient outcomes. The data will be used to further evaluate and analyze patient outcomes from SIR-Spheres® therapy.

In addition, de-identified, aggregate data may be used in discussions with regulatory authorities, public and private payers/insurers, policy-makers, and others.

- Complications identified through analysis of the Registry data will be reported to Sirtex's Quality Assurance function and addressed in accordance with Sirtex policy and reported to the FDA in accordance with legal and regulatory requirements.

4. **Therasphere HDE**

- A Humanitarian Device Exemption Use Protocol of TheraSphere or Treatment of Unresectable Hepatocellular Carcinoma
- Post-Marketing: TheraSphere commercially distributed under HDE # 980006
- Objectives-Provide supervised access to TheraSphere therapy at this institution, evaluate response to treatment, toxicities and adverse experiences associatedwith TheraSphere treatment, and survival time
- Endpoints- Proportion of patients completing scheduled treatment plan,
- Efficacy: Response to Treatment, Survival Time from First Treatment
- Safety: Adverse Experiences

The research team did not submit a list of publications and presentations.

Inova Neurosciences research program aspires to be an international leader in clinical and basic research for disorders of the brain and nervoussystem, to pro vide training for future neuroscientists and clinicians, and to ensure that Inova's Department of Neurosci ences provides the best possible clinical care for our community. We hope to continually improve the care we provide for our patients through analysis of patient outcomes from current practices, and through front-end involvement in new clinical research interventions.

In the fall of 2007, the departments of Neurology and Neurosurgery joined to form the new Department of Neurosciences under the leadership of Dr. James Eck lund, Chairman of the Department of Neurosciences at Inova Fairfax Hospital.

Being the only Level 1 Trauma Center in the region, Inova Fairfax Hospital cares for a large population of people who have suffered head injuries. Current research opportunities include several potential drug trials aimed at decreasing secondary injury related to the physiologic responses to head injury.

The Stroke Program was ranked this year as among the top 5% of hospitals in the nation for treatment of stroke and ranked "Best in Virginia for Treatment of Stroke." This program provides the opportunity to per form cutting-edge research to benefit our patients and community, including drug, endovascular, and surgical treatments for stroke as well as secondary prevention interventions.

Future areas of research include comparative outcomes measurements, neuro-oncology trials, genomic and proteonomic strategies to provide person alized medical treatments, and regenerative and functional restoration programs to decrease disability from several diseases including dementia.

The Neuroscience department carried out four funded and five unfunded protocols. The following are publica tions and presentations from the Department of Neuro science.

BOOKS, BOOK CHAPTER, AND JOURNAL ARTICLES

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3. Tian F, Hu XZ, Wu X, Jiang H, Pan HN, Marini AM, Lipsky RH 2009. Dynamic chromatin remodeling events in hippocampal neu rons are associated with NMDA receptor-mediated activation of Bdnf gene promoter 1. Amino Acids 37: 15-16, Suppl 1.
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5. Blondeau N, Nguemeni C, Debruyne DN, Piens M, Wu X, Pan H, Hu X, Gandin C, Lipsky RH, Plumier JC, Marini AM, Heurteaux C 2009. Subchronic alpha-linolenic acid treatment enhances brain plasticity and exerts an antidepressant effect: a versatile potential therapy for stroke. Neuropsychopharmacology. 34:2548-2559.
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14. Ling G, Bandak F, Armonda R, Grant G, Ecklund J 2009. Explosive blast neurotrauma. J Neurotrauma. 26:815-825.
15. Lipsky RH, Hu XZ, Goldman D 2009. Additional functional variation at the SLC6A4 gene. Am J Med Genet B Neuropsychiatr Genet. 150B:153.
16. Roecklein KA, Rohan KJ, Duncan WC, Rollag MD, Rosenthal NE, Lipsky RH, Provencio I 2009. A missense variant (P10L) of the melanopsin (OPN4) gene in seasonal affective disorder. J Affect Disord. 114:279-285.
17. Salous AK, Ren H, Lamb KA, Hu XQ, Lipsky RH, Peoples RW 2009. Differential actions of ethanol and trichloroethanol at sites in the M3 and M4 domains of the NMDA receptor GluN2A (NR2A) subunit. Br J Pharmacol. 158:1395-1404.
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4. Ecklund J. Functional restoration through robotics. AANS/CNS Section on Disorders of the Spine and Peripheral Nerves Annual Meeting. Phoenix, AZ; March, 2009.
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7. Ecklund J. Neurosurgical treatment of blast induced neurotrauma: Observations from the global war on terrorism. Fourteenth Euroacademia Multidisciplinaria Neurotraumatologica Congress. Kaunas, Lithuania; June, 2009.
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9. Khalil M, Wulfkuhle J, Fillmore H, Deng J, Liotta L, Petricoin III E, Watson J, Broaddus W 2009. Functional pathway mapping of h uman glioblastoma multiforme and brain metastases for patient tailored therapy. J Clin Oncology 27: 15S.
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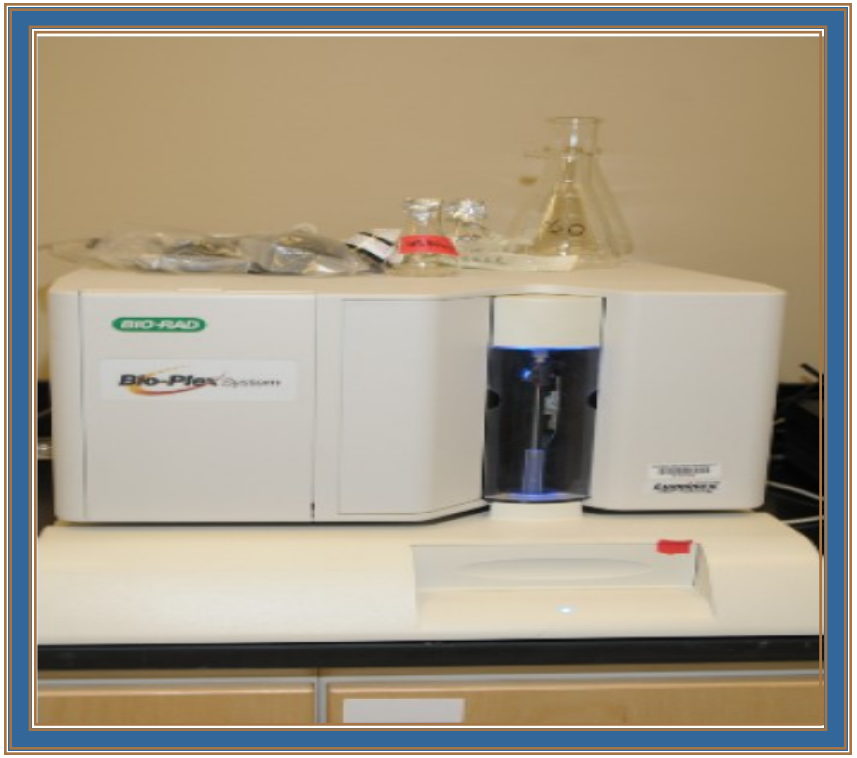

In 2009, the Inova Health System (IHS) Nursing Research Committee (NRC) continued to expand and solidify the infrastructure required to support nursing research excellence. The NRC includes a representative from each hospital-based research committee as well as representatives from George Mason University, the Inova Research Center, the Medical Library, the Inova Learning Network, Epidemiology and Biostatistics, and the Department of Professional Practice.

The Inova Health System Nursing Research Internship program was launched in the first quarter of 2008, funded by both Inova Health System and a philanthropic donor interested in pursuing Human Caring nursing research. Through a competitive application process in 2009, ten nursing research internships were awarded across five Inova Health System hospitals. During their internship, these research interns were introduced to the research process and mentored through completion of a nursing research study. The majority of study projects focus on strategies to improve patient outcomes and the nursing work environment.

The NRC continues to add to a system-wide repository for nursing research activity utilizing a shared drive and an access database. Productivity reports are available for both the system and the operating unit level. In addition, formal guidelines were finalized to support non-Inova Health System researchers conducting nursing research in collaboration with an Inova Health System registered nurse, enabling expanded partnerships with local university graduate programs. The NRC continues to benefit from established Inova resources in grant writing and statistician support.

In 2009, NRC coordinated the 6th Annual Fall Into Nursing Research conference. The all-day conference included internal and external faculty presenting on a wide range of research topics, including the research process and presentation of research findings. A research poster symposium with over twenty displays was also part of the day's activities. In addition to the annual research conference, the NRC coordinated two 2-day research workshops, aimed at increasing the skill of the novice nurse researcher. In collaboration with the Inova Learning Network and IHS Professional Practice, the NRC co-hosted a one-day workshop on preparing nursing manuscripts for publication. This writer's workshop was presented by the editorial staff of the *American Journal of Nursing*, and included guidance on dissemination of research findings through publication.

BOOKS, BOOK CHAPTERS, AND JOURNAL ARTICLES

1. Sheree O'Neil, Karen Gabel Speroni, Lisa Dugan, & Marlon Daniel. A Two-tier Study of Direct Care Providers Assessing the Effectiveness of the Red Rule Education Project and Precipitating Fac tors Surrounding Red Rule Violations. In press, Journal of Quality Management in Health Care. Spring 2010 issue, 19:2.
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3. Klein, L, Howard, S, Abisogun, L, Owusu, E, & Connell, R. Effectiveness of parent education on late preterm infants' readmission rates. Sixth Annual "Spring Into Nursing Research. Reston Hospital Center Research 2009.
4. Klein, L, Howard, S, Abisogun, L, Owusu, E, & Connell, R. Effec tiveness of parent education on late preterm infants' readmission rates. Sixth Annual Fall into Research Conference, Research Into Practice and Practice Into Research 2009.
5. Vourlekis, JS & Schakenbach, L (2008). Community hospital experience with therapeutic hypothermia after cardiac arrest. *Critical Care Medicine*; 36 (12 Suppl):A145.
6. Henry LL, Martin LM, Hunt SL Barnett SD, Ad N. The Impact of Coronary Artery Bypass Graft Surgery on the Physical Functioning of the Aged. Circulation [online]; TBD
7. Henry LL, Martin LS, Hunt S, Barnett S, Halpin L, Ad N. The Association of Survival and Patient Disposition Following Coronary Artery Bypass Surgery. Circulation [online]; TBD
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13. Hack, C., Speroni, K. Gabel, & Earley, C. Preliminary Analysis of the Evaluation of the Prevalence of Methicillin-Resistant Staphylococcus Aureus Colonization in Pre-surgical Patients and Post-Operative Infection. Sixth Annual "Spring Into Nursing Research". Reston Hospi tal Center Research Committee 2009.
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23. Taylor, B, Speroni, K. Gabel, Earley, C., Andrejasich, C., & Daniel, M. Community Health Survey Research Study Evaluating Factors Linked To Breastfeeding Choices. First Annual Nursing Scholar ship Virtual Exhibition,Washington Regional Nursing Research Consortium 2009.
24. Taylor, B, Speroni, K. Gabel, Earley, C., Andrejasich, C., & Daniel, M. Community Health Survey Research Study Evaluating Factors Linked To Breastfeeding Choices. Shenandoah University Division of Nursing, 10th Annual Research Symposium 2009.

LECTURES AND FACULTY PRESENTATIONS TO NATIONAL/ INTERNATIONAL MEETINGS

1. Sedlemeyer, J., Phelan, A., & Brundage, J. Research presentation: human caring study. Inova Health System Nursing Research Work shop 2009.
2. Bergin, C, Kelly, K, Travis, T. & Speroni, K. Interim Analysis: POISE Study (Pre-operative Incentive Spirometry Education). Sixth Annual Fall into Research Conference, Research Into Practice and Practice Into Research 2009.
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4. Carnes, A. & Guise, S. “Positive Motivation: Using a Safety Concept in Education.” American Association of Diabetes Educators 36th Annual Meeting 2009.
5. Hack, Cindy. Preliminary Analysis of the Evaluation of the Prevalence of Methicillin-Resistant Staphylococcus Aureus Colonization in Pre-Surgical Patients and Post-Op Infections. Shenandoah University Division of Nursing, 10th Annual Research Symposium 2009.
6. Harrison, Gina. Emergency Medical Services Blood Specimen Quality versus Emergency Department Staff. Emergency Nurses Asso ciation 2009 Annual Conference 2009.
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8. Speroni, K.Gabel. “Kids Living Fit (KLF) Childhood Obesity Research Program”. Magnet: Inspiring Innovation, Achieving Out comes 2009 ANCC National Magnet Conference 2009.
9. Speroni, K.G. & McLaughlin, M. “Hospital-Based Nursing Research Requirements and Outcomes Survey”. Magnet: Inspiring Innovation, Achieving Outcomes 2009 ANCC National Magnet Conference 2009.
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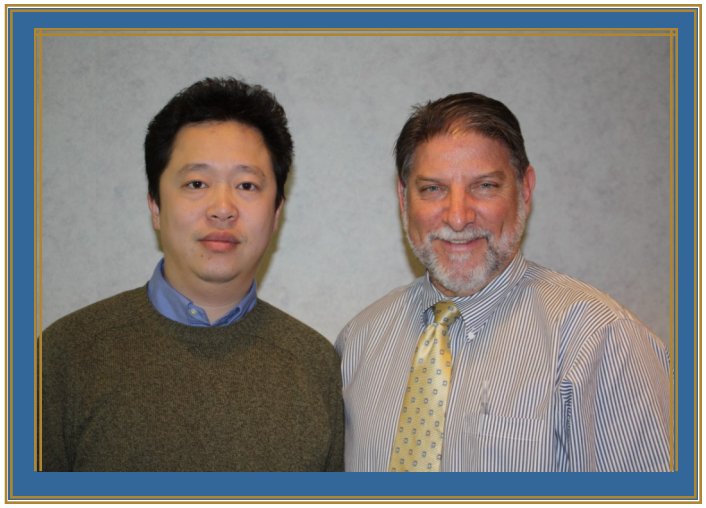

The Biomechanics Research Laborabory of the Department of Orthopaedics at Inova Fairfax Hospital has four broad goals: 1) Foster biomechanical and clinical research among ortho paedic surgeons and help them to solve complex clinical problems; 2) Apply the principles of mechanics and biology to understanding basic mechanisms related to the structure and func tion of the musculoskeletal system; 3) Design, analyze, and develop bone-implant and pros thetic systems; and 4) Educate residents in performing independent, high-quality research in orthopaedic biomechanics.

The Biomechanics Research Laboratory is dedicated to the discovery and development of biomechanical solutions for a broad array of clinical specialties, such as total joint replace ment, orthopaedic trauma injuries, sports injuries, arthroscopic surgery, orthopaedic oncol ogy, spine surgery, and pediatric orthopaedic surgery. The laboratory is equipped with state-of-the-art equipment to investigate the failure mechanism of musculoskeletal-implant con structs, help physicians to make best clinical decisions, and design new implants and surgi cal methods.

Computer simulation is becoming a critical and valuable technique for helping orthopaedic physicians with complicated cases. Inova Fairfax Hospital's Biomechanics Research Labora tory is equipped with powerful computer workstations and advanced software for computer simulation and analyses of complex musculoskeletal-implant constructs. The computer helps physicians generate patient specific 3D geometric models based on CT/MRI images, perform virtual orthopedic surgery on the patients' computer model, analyze the construct strength, and evaluate the potential for long term implant survival. With this state-of-the-art capability, Inova Fairfax Hospital's orthopaedic patients can have their proposed surgery performed and analyzed by computer prior to undergoing actual surgery to provide the best possible out come.

The Biomechanics Research program at Inova Fairfax Hospital finished two projects in 2009:

- Effect of Bone Quality on the Failure of Locked Plate Fixation of Proximal Humerus. Jihui Li, Robert Hymes, Jeff Schulman, Mark Theiss. Funded by: Inova Faculty Research Grant and Smith & Nephew Inc.
- Biomechanical Comparison of Two Types of Fixation of Ludloff Metatarsal Osteotomies: Compresion Screws vs. Locking Plate. Steve Neufeld, Jihui Li Funded by: Merete Inc. and Synthes Inc.

They have recently received four funded projects:

- Acoustic Emissions Testing for Occult Pediatric Fractures and Stress Fractures. Kathleen McHale, Juhui Li, Mark Theiss, Samuel Hawken, Funded by: Inova Foundation.
- The Development of VKASS: A Virtual Knee Anatomy and Surgery System. Jim Chen, Jihui Li, Mark Theiss, Craig Cheifetz, Funded by: George Mason-Inova Research Fund.
- Patient Specific 3-D Medical Modeling Can Improve Preoperative Surgical Planning of Complex Spinal Orthopedic Cases. Faisal Siddiqui, Jihui Li, Ali

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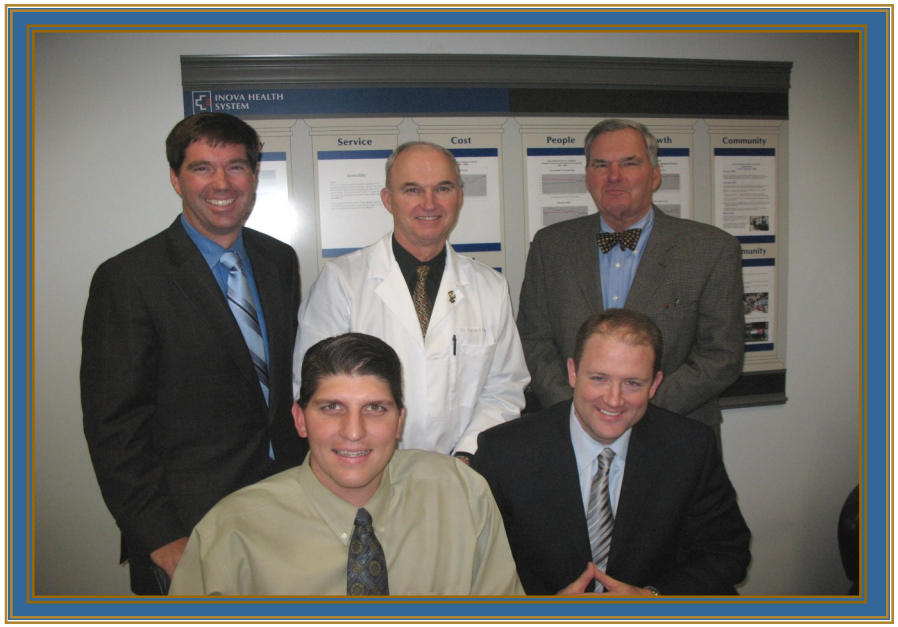
1. Jihui Li, Robert Hymes, Jeff Schulman, Mark Theiss, Monitoring the Fatigue Procedure of Proximal Humeral Fracture Fixation Using Acoustic Emission Technique. 52nd Meeting of Acoustic Emission Working Group in Sturgeon Bay, Wisconsin, October 19 21, 2009.
2. Jihui Li, Felasfa Wodajo, Patient-Specific Finite Element Analysis of Femoral Giant Cell Tumor Reconstructed Using Locking Plate System. 11th ASME Summer Bioengineering Conference, Lake Tahoe, California June 17-21, 2009.
3. Clinical Efficacy and Functional Outcomes of Autologous Bone Grafting from the Distal Femur and Proximal Tibia for Fracure Non-unions. Robert A. Hymes, Timothy Ryan, Cary Schwartzbach, Stephen Malekzadeh, Feff Schulman. Poster at 2009 OTA Annual Meeting, San Diego, CA.
4. Jihui Li, Applications of Acoustic Emission in Orthopaedic & Biomechanical Research. 52nd Meeting of Acoustic Emission Working Group in Sturgeon Bay, Wisconsin, October 19 - 21, 2009.



Working collaboratively with the Joint Replacement Center at Inova Mount Vernon Hospital, the Anderson Orthopaedic Research Institute (AORI) continues to generate clinically-relevant research related to hip and knee joint replacements. The goal of this collaborative research is to improve the quality of life for both current and future joint replacement patients.

With every joint replacement innovation comes the need to determine how the new technology affects clinical outcome. To evaluate new bearing surfaces and implant designs, AORI is conducting several prospective, randomized clinical trials. AORI also maintains an institutional joint registry database that enables retrospective outcome analyses. In a study that was published during the past year using this database, AORI researchers found that a contemporary third-generation hip replacement design significantly reduced the incidence periprosthetic bone loss (known clinically as osteolysis) compared to a second-generation design that had been used predominantly from 1990 through 2000.

AORI researchers also continue to publish clinical outcome studies related to the use of porous-coated fixation for hip replacements, a technology that was pioneered by Dr. Charles Engh at AORI over 30 years ago. Among knee replacement patients, AORI is working to measure implant wear and determine factors that influence the wear process. AORI is also developing more sensitive techniques for quantifying outcomes after knee replacement. These techniques, including analyses of patient gait and balance, provide objective outcome data enabling improved comparisons of implant designs.

Recognizing that joint replacement patients now routinely expect 20 to 30 years of service from their implants, AORI's current research also focuses on understanding the mechanisms that lead to long-term implant failure, including wear and bone loss. Using three-dimensional imaging modalities, like computed tomography (CT), AORI is working to improve the diagnosis and treatment of bone loss around joint replacements.

To ensure that their research findings are available to the world-wide orthopaedic community, AORI-affiliated physicians publish their studies in medical journals and present their findings at national and international orthopaedic meetings. In 2009, AORI's collaboration with Inova yielded 11 publications in peer-reviewed orthopaedic journals. In addition, 32 talks and two posters were presented at major scientific meetings

BOOKS, BOOK CHAPTERS AND JOURNAL ARTICLES

1. Egawa H, Powers CC, Beykirch SE, Hopper RH Jr, Engh CA Jr, Engh CA Sr. Can the Volume of Pelvic Osteolysis be Calculated without Using Computed Tomography? Clinical Orthopaedics and Related Research. Published January 2009;467:181-187
2. Engh CA Jr, MacDonald SJ, Sritulanondha S, Thompson A, Naudie D, Engh CA Sr. Metal Ion Levels After Metal-on-Metal Total Hip Ar throplasty: A Randomized Trial Clinical Orthopaedics and Related Research. Published January 2009;467:101-111
3. Rao AN, Engh JA, Engh GA, Parks NL. Mechanical Stability of Well-Functioning Tibial Baseplates from Postmortem-Retrieved Total Knee Arthroplasties. Journal of Arthroplasty Published February 2009 [Epub ahead of print]
4. Egawa H, Ho H, Hopper RH Jr, Engh CA Jr, Engh CA Sr. Computed Tomography Assessment of Pelvic Osteolysis and Cup-Lesion Inter face Involvement with a Press-Fit Porous-Coated Acetabular Cup. Journal of Arthroplasty Published February 2009;24(2):233-239

5. El-Yussif E, Engh GA. A Technique for Lateral Unicompartmental Arthroplasty: A Road Less Traveled. Published March 2009;20(1):6-10
5. Engh CA Sr. Newer Radiographic Methods for Detection and Trea tment Planning for Patients with Pelvic Osteolysis. Seminars in Ar throplasty Published March 2009;20(1):66-76
6. Powers CC, Ho H, Beykirch SE, Huynh C, Hopper RH Jr, Engh CA Jr, Engh CA Sr. A Comparison of a Second and a Third Generation Modular Cup Design: Is New Improved? Journal of Arthorplasty Publ ished April 2009 [Epub ahead of print]
7. Engh CA Jr, Mohan V, Nagowski JP, Sychterz-Terefenko CJ, Engh CA Sr Influence of Stem Size on Clinical Outcome of Primary Total Hip Arthroplasty with Cementless Extensively Porous-Coated Femo ral Components. Journal of Arthorplasty Published June 2009;24(4);554-9
8. Hamilton WG, Ammeen D, Engh CA Jr, Engh GA. Learning Curve with Minimally Invasive Unicompartmental Arthroplasty. Journal of Arthorplasty Published July 2009 [Epub ahead of print]
9. Engh GA, Zimmerman RL, Parks NL, Engh CA Jr. Analysis of Wear in Retrieved Mobile and Fixed Bearing Knee Inserts. Journal of Arthro plasty/Proceedings from 2008 AAHKS meeting Published September 2009; 24(6 Suppl):28 - 32.

ABSTRACTS AND PRESENTATIONS TO NATIONAL/INTERNATIONAL MEETINGS

1. Engh GA, Engh CA Jr, Zimmerman R, Parks N. Wear in Retrieved Mobile Bearing and Fixed Bearing Knee Inserts. Presented by Gerard A. Engh, MD on 1/16/09 in St. Thomas, USVI
2. Engh CA Sr. Newer Radiographic Methods for Detection, Evaluation and Treatment of Pelvic Osteolysis. Presented by Dr. Charles A. Engh, Sr MD on 1/16/2009 in St. Thomas, U.S.V.I
3. Engh GA. Philosophy and Results with UKA and Bicompartmental Arthroplasty. Customized Instrumentation. AAOS 2009 Instructional Course Lecture Presented by Gerard A. Engh on 2/25/09
4. Zimmerman RL, Engh GA, Parks NL, Engh CA Jr. Analysis of Wear in Retrieved Mobile and Fixed Bearing Knee Inserts. AAOS 2009 An nual Meeting, Las Vegas, Nevada Presented by Rebecca Zimmer man on 2/25/2009
5. Engh GA, Sheridan MJ, Ammeen D. A New Method for Measuring Function with Knee Arthroplasty Surgery. 2009 American Academy of Orthopaedic Surgeons Annual Meeting (Podium Presentation #254), Las Vegas. Presented by Gerard A. Engh on 2/26/09
6. Engh CA Jr. Head and Liner Exchange for Osteolysis: Results, indi cations, technical tips to avoid complications of a common proce dure. 2009 American Academy of Orthopaedic Surgeons Annual Meeting-Hip Society Specialty Day Presented by C. Anderson Engh Jr., M.D. on February 28, 2009 in Las Vegas, Nevada
7. Engh GA. Alternate Allograft Techniques in Revision Total Knee Arthroplasty. Current Concepts in Joint Replacement - Spring Meet ing, Las Vegas, NV Presented by Gerard A. Engh, MD on May 18, 2009
8. Engh GA UKA: Past, Present & Future (Keynote Address). 3rd An nual Contemporary Issues in Partial Knee Arthroplasty, New Albany Surgical Hospital Presented by Gerard A. Engh, MD on 10/16/09
9. Engh GA. Minimally Invasive Medial UKA: Pitfalls & Complications 3rd Annual Contemporary Issues in Partial Knee Arthroplasty, New Albany Surgical Hospital Presented by Gerard A. Engh, MD on 10/17/09
10. Engh CA Sr. Metal-on-Metal Hip Replacement: Anderson Clinic Ex perience. Follow the Future: Tissue Guided Surgery and Other Trends in Joint Arthroplasty Engh Society Presented by Charles A. Engh, Sr. M.D. on 10/22/2009 in Alexandria, Virginia
11. Engh CA Sr, Engh CA Jr, Ho H, Beykirch SE, Powers CC, Hopper RH Jr 10yr Results of a 2nd Generation Modular Hip System. Fol low the Future: Tissue Guided Surgery and Other Trends in Joint Arthroplasty Engh Society Presented by Charles A. Engh, Sr. M.D. on 10/22/2009 in Alexandria, Virginia
12. Engh GA. Philosophy and Results with Bicompartmental Arthro plasty Follow the Future: Tissue Guided Surgery and Other Trends in Joint Arthroplasty Engh Society Presented by Gerard A. Engh on 10/22/09 in Alexandria, Virginia
13. Engh CA Jr, Engh CA Sr, Hopper RH Jr, Ho H, Beykirch SE. An Evaluation of the Differences in Wear Between Crosslinked Mara thon and Non-Crosslinked Enduron Polyethylene 39th Annual Ad vances in Arthroplasty Presented by Charles A. Engh, Sr. M.D. on 10/28/2009 in Boston, Massachusetts.
14. Engh CA Sr Metal-on-Metal Hip Replacement: Anderson Clinic Ex perience 39th Annual Advances in Arthroplasty Presented by Charles A. Engh, Sr. M.D. on 10/28/2009 in Boston, Massachusetts
15. Engh CA Sr CT vs. Plain Films to Evaluate Lysis: When and Why 9th Annual Advances in Arthroplasty Presented by Charles A. Engh,

Sr. M.D. on 10/28/2009 in Boston, Massachusetts

16. Engh CA Sr, Belmont PJ Jr, Powers CC, Beykirch SE, Hopper RH Jr The AML Hip at 20 Years 39th Annual Advances in Arthroplasty Presented by Charles A. Engh, Sr. M.D. on 10/28/2009 in Boston, Massachusetts
17. Engh CA Sr, Engh CA Jr, Ho H, Beykirch SE, Powers CC, Hopper RH Jr. 10-Year Results of a 2nd Generation Modular Hip System 39th Annual Advances in Arthroplasty Presented by Charles A. Engh, Sr. M.D. on 10/28/2009 in Boston, Massachusetts
18. Hamilton WG, Hopper RH Jr, Engh CA Jr, Engh CA Sr. Polyethyl ene Liner Exchange for Wear and Osteolysis Among Porous-Coated Cups 19th Annual American Associations of Hip & Knee Surgeons Meeting Presented by William G. Hamilton on 11/7/09 in Dallas, Texas
19. Engh CA Jr. Patient Specific Knee Instruments. Bioskills Confer ence Presented by C. Anderson Engh Jr., M.D. on 12/4/09
20. Engh Sr CA. Metal- Metal Hip Replacement: Anderson Clinic Ex perience. Reston Grand Rounds Presented by Charles A. Engh, Sr. M.D. on 12/9/2009 in Reston, Virginia
21. Engh GA. Total Knee Revision: A Day in the Life of…Current Con cepts in Joint Replacement - Winter 2009, Orlando, FL Presented by Gerard A. Engh, MD on 12/12/09
22. C. Anderson Engh Jr., M.D. Patient Specific Knee Instruments. Washington Orthopaedic Society Presented by C. Anderson Engh Jr., M.D. on 12/14/2009

Inova Fairfax Hospital for Children is committed to providing excellence in pediatric health care by providing the highest quality care, exemplary medical education, and innovative research practice to care for children.

ACADEMIC PRODUCTIVITY AND RESEARCH STUDIES

During the past year, the Department of Pediatrics has continued to develop and support a varied and diverse research focus. These efforts have led our faculty to write a number of published or accepted papers as well as book chapters, and national presentations in 2009.

Research activities include national patient registries and database participation to continually benchmark and utilize evidence based practice initiatives to drive clinical outcomes. Gastroenterology, emergency medicine, pediatric critical care, and neonatal critical care have taken leadership roles within these national collaboratives and promote research activities in these areas of specialty. The pediatric research efforts are as varied and diverse as the patient population. The critical care team has focused on clinical drug studies, establishing national benchmarks in hospital acquired infections and neonatal/pediatric resuscitation efforts, as well as neurodevelopmental outcomes and interventions. Gastroenterology works with bench science to evaluate the role of cellular immunity and clinical practice, and functions as a key participant in several inflammatory disease studies. Quality research endeavors are being pursued in a rich multidisciplinary team approach. The pediatric department remains involved in projects of wide ranging topics including nephrology, cardiology, surgery, cardiac surgery, international adoption, and infectious diseases.

The Department of Pediatrics continues to promote the development of residents and fellows through structured research education and dedicated research mentors. In 2009, our pediatric residents published or presented a number of journal articles, book chapters, and abstracts at such prestigious pediatric national meetings as the Pediatric Academic Society and American Academy of Pediatric Annual Meeting.

By facilitating research innovation of the next generation of pediatricians, we ensure the continued excellence in specialty health care delivery for the children of the region. The ongoing improvement and growth focusing on translational research and clinical outcomes will continue to help identify Inova Fairfax Hospital for Children as one of the leading Children's hospital and research centers.

BOOKS, BOOK CHAPTERS, AND JOURNAL ARTICLES

1. Baron, I.S., Ahronovich, M.D., Erickson, K., Gidley Larson, J. C., & Litman, F. (2009) Age-Appropriate Early School Age Neurobehavi oral Outcomes of Extremely Preterm Birth Without Severe Intraven tricular Hemorrhage: A Single Center Experience, Early Human De velopment, 85, 191-196.
2. Baron, I.S., Erickson, K., Ahronovich, M. D., Coulehan, K., Baker, R., and Litman, F. R. (2009) Visuospatial and Verbal Fluency Rela tive Deficits in 'Complicated' Late-Preterm Preschool Children. Early Human Development, 85, 751-754.
3. Gidley Larson, J. C., Baron, I. S. , Ahronovich, M. D., and Iampietro, M., (in press) Micropremature Birth. In Morgan, J., Baron, I.S., & Ricker, J. (Eds.). Casebook of Clinical Neuropsychology, New York: Oxford University Press.
4. Newton, P., Kamat- Nerikar, R. (2009). Answer to the photo quiz: A 10- year old girl with a rash and abdominal pain. Clinical Infectious Diseases, 48, 683-684.
5. Troy R, Doron M, Laughon M, Tolleson-Rinehart S, Price W. Com parison of noninvasive and central arterial blood pressure measure ments in ELBW infants. J. Perinatology 2009; 29: 744-749.

6. Wijetilleke, A., Sakran, M., Kamat- Nerikar, R. (2009). Vomiting in a girl with Autism. Clinical Pediatrics, 48(2), 224-227.
7. Howell JM, Dugan EM: Breast Masses and Breast Infection. The Clinical Practice of Emergency Medicine, 5th ed, Wolfson A.B., et al (eds); Lipponcott, Williams and Wilkins, Philadelphia, PA, 2009 (In press).
8. Howell JM: Critical issues in the evaluation and management of emergency department patients with suspected appendicitis. ACEP News (In press).

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1. Coulehan, K., Erickson, K., Ahronovich, M.A., Litman, F.R., and Baron, I.S. Early School-age Executive Functioning of Extremely Low Birth Weight Infants with Bronchopulmonary Dysplasia. Journal of the International Neuropsychological Society, Volume 15, Supplement S1, February 2009, Cambridge University Press.
2. Ahronovich, M., Erickson, K., Litman, F. and Baron, I.S. Effects of Dexamethasone Duration on Neurocognitive Outcome at Six Years. (2009) Acta Paediatrica, 98, 72-73, Suppl. 460.
3. Baron, I.S. Erickson, K. Fletcher, A.A. Coulehan, K. Iampietro, M. Ahronovich, M.A. & Litman. F.R. Neurobehavioral and Cognitive Out comes of Extremely Preterm, Late Preterm, and Term Birth at Three-Years-Old: A Single Center Study. Presented at Symposium entitled "The nature of neurobehavioral impairments in children born very preterm" at the 37th Annual International Neuropsychological Society Meeting, Atlanta, GA, February 2009.
4. Meltzer AC, Osborn S, Howell JM, Cummings DAT, Place R, Druck enbrod G. Identification clinical characteristics in emergency depart ment triage that predict the need for administration of oral contrast for abdominal cat scan. International Conference: Caribbean Emer gency Medicine Congress Jan 2009
5. Meltzer AC, Place R, Cummings DAT, Solomon B, Howell JM. Risk of serious bacterial infection in febrile infants with influenza. International Conference: Caribbean Emergency Medicine Congress Jan 2009
6. Place RC, Herr S. Pediatric Emergency Department Throughput: A comparison of door to provider times at nine institutions. NACHRI & N.A.C.H. 2009 Creating Connections Conference. (Accepted as Poster Presentation). March 2009
7. Lashkeri T, Howell JM, Place R. Capnometry as a predictor of admissions in bronchiolitis. Society of Academic Emergency Medicine: National Meeting, May 2009, New Orleans LA. (Also presented at Pediatric Academic Societies Annual Meeting, May, 2009, Baltimore, MD)
8. Ali AB, Place R, Howell J, Malubay S, Issaev C. Reasons for early emergency department return visits: a prospective assessment. Society of Academic Emergency Medicine: National Meeting, May 2009, New Orleans, LA (Also presented at Pediatric Academic Societies Annual Meeting, May, 2009, Baltimore, MD)
9. Place RC, Layman K, Neuner M, Choppard M, Howell JM. Ambulatory prescription errors in a pediatric emergency department. American College of Emergency Physicians National Assembly. Oct 2009, Boston MA
10. Place RC, Kou M, Howell JM. An analysis of prolonged length of stay in a pediatric emergency department. American College of Emergency Physicians National Assembly. Oct 2009, Boston MA
11. Meltzer AC, Osborn S, Howell JM, Cummings DAT, Place R, Druck enbrod G. Identification clinical characteristics in emergency depart ment triage that predict the need for administration of oral contrast for abdominal cat scan. International Conference: Caribbean Emergency Medicine Congress Jan 2009
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16. Lashkeri T, Howell JM, Place R. Capnometry as a predictor of ad missions in bronchiolitis. Society of Academic Emergency Medicine: National Meeting, May 2009, New Orleans LA. (Also presented at Pediatric Academic Societies Annual Meeting, May, 2009, Baltimore, MD)

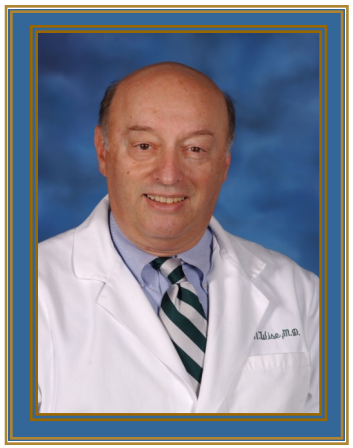
PAGE 56 PEDIATRICS CONTINUED

17. Davis J, Churosh N, Borloz M, Howell J. "Knowledge of Self-injectable Epinephrine Technique Among Emergency Medical Services Providers (abstract # 112)". 2009 ACEP Scientific Assembly. Ann Emerg Med 2009; Sept (54: 3, Supplement S36).
18. Badalyan, V. Management of Congenital preauricular sinus: A survey of members of the American Society of Pediatric Otolaryngology. Striving for Excellence in Research and Clinical Thinking: A symposium for Pediatric Residents, Jacksonville, FL 2009
19. Ghazirad, M. Antropometic measurements and gestational age as predictors of care safety seat test failure in late- preterm and low birth weigh infants. A symposium for Pediatric Residents, Jacksonville, FL 2009
20. Lashkeri, T. Capnometry as a Predictor of Admissions in Bronchiolitis. SAEM 2009 Annual Meeting. New Orleans, LA Allard, B., Klein, J., Beck, J., Lazarte, R and Carpenter, K.R. Lateral Transport of Neonates from Level III Nursery to a Pediatric Hospitalist Service. Pediatric Hospital Medicine. Tampa, FL 2009

LECTURE AND FACULTY PRESENTATIONS TO NATIONAL OR INTERNATIONAL MEETINGS

1. Ali, A. Reasons for early emergency department return visits: a prospective assessment, 2009 Eastern Society for Pediatric
2. Research Annual Meeting, Philadelphia, PA- March 2009.
3. Fish, S. Donnelly, K. Resident. Led quality improvement effort succeeds in increasing medication ordering compliance, 2009 Eastern Society for Pediatric Research Annual Meeting, Philadelphia, PA-March 2009.
4. Harmelin, M. Language acquisition in internationally adopted children. 2009 American Academy of Pediatrics (AAP)
5. National Conference and Exhibition, Washington, DC -October 2009
6. Mason, P. A comparative study of the tuberculosis skin test and QuantifFERON- TB Gold Assay in children Adopted internationally. 2009 American Academy of Pediatrics (AAP)
7. National Conference and Exhibition, Washington, DC -October 2009
8. Narad, C. Parental stress following international adoption. 2009 American Academy of Pediatrics (AAP)
9. National Conference and Exhibition, Washington, DC -October 2009
10. R Place. “Meeting the Needs of the Evolving Workforce in Pediatric Emergency Medicine”, panelist, Pediatric Academic Societies Annual Meeting, May, 2009, Baltimore, MD
11. R Place.“Caustic and Hydrocarbon Ingestions”, Clinical Decision-making in Emergency Medicine Jun, 2008, Ponte Vedre, FL
12. R Place. “Pediatric Trauma”, Advanced Pediatric Life Support; American Academy of Pediatrics, National Conference; Oct, 2009; Washington, DC
13. Maybelle Kou. Advanced Pediatric Life Support: The Pediatric Emergency Medicine Course; American Academy of Pediatrics National Conference. Washington DC. October 17th, 2009.
14. Ngo, T., Dockery, W.K. Safety and efficacy of intravenous Ketorolac in infants and children following cardiac surgery. 2009 American Academy of Pediatrics (AAP)National Conference and Exhibition, Washington, DC -October 2009
15. Schwartz, R. Tympanic membrane retraction pockets: Appearance, diagnosis, and complications. 2009 American Academy of Pediatrics (AAP) National Conference and Exhibition, Washington, DC -October 2009
16. Allard, B., Badalyan, V., Leibowitz, I. A 15-year old Female with Adenocarcinoma of Colon. NASPGHAN Annual Meeting November, 2009
17. Badalyan, V., Schwartz, R. A survey of feeding and gastrointestinal problems in children with autistic spectrum disorders: comparison with their normally developing siblings. NASPGHAN Annual Meeting.November, 2009
18. Badalyan, V., Leibowitz, I., Lazarte, R. Diagnosis and treatment of gastro- esophageal reflux in neonatal intensive care unit. NASPGHAN Annual Meeting. November, 2009
19. Jimenez, J., Nzegwu, N., Enav, B., Duffy, L., Louis-Jacques, O., Lee, P., Chao, C., Kim, S., Schorin, M., Loncar, D., Johal, J., Leibowitz, I. Chronic Diarrhea: Pancreatic VIPoma in an 11 Year-Old Male. NASPGHAN Annual Meeting.November, 2009
20. Allard, B., Carpenter, K. Lateral transport of neonates from a level III Nursery to a pediatric hospitalist service. Hospital Medicine SIG 2009 PAS Meeting. Platform Presentation
21. Troy, R. Poster presentation: North Carolina Quality and Patient Safety Conference, March, 2009 “Saving Eyes and Lungs (SEAL): Oxygen Saturation Limits in the NICU”, Chapel Hill, NC.
22. K Fullerton. Advanced Pediatric Life Support: The Pediatric Emergency Medicine Course; American Academy of Pediatrics National Conference. Washington DC. October 17th, 2009.
23. M CamarcaFaculty. Advanced Pediatric Life Support: The Pediatric Emergency Medicine Course; American Academy of Pediatrics National Conference. Washington DC. October 17th, 2009.

24. B D'Cruz. Advanced Pediatric Life Support: The Pediatric Emergency Medicine Course; American Academy of Pediatrics National Conference. Washington DC. October 17th, 2009
25. D Pauze. Advanced Pediatric Life Support: The Pediatric Emergency Medicine Course; American Academy of Pediatrics National Conference. Washington DC. October 17th, 2009.
26. S Miller. Decision Making Under Pressure: Lessions from the ER, George Washington University Luther Rice Society's Financial Alliance Luncheon, New York, NY, Mar 2009
27. S Miller. Decision Making, George Washington University Department of Organizational Sciences & Communication, Feb 2009
28. JM Howell."Soft Tissue Infections in the Age of MRSA: What You Should Know." Clinical Decision Making in Emergency Medicine, Ponte Vedra, Florida, June 25, 2009.
29. JM Howell. "Pain Management in the ED: Taking the pain out of the emergency (panel discussant)." Clinical Decision Making in Emergency Medicine, Ponte Vedra, Florida, June 26, 2009.
30. JM Howell. "Advanced Pediatric Life Support (Medical Emergencies and Office Based Emergencies)." American Academy of Pediatrics Annual Symposium, Washington, D.C., October 17, 2009.
31. JM Howell. Faculty. Advanced Pediatric Life Support: The Pediatric Emergency Medicine Course; American Academy of Pediatrics National Conference. Washington DC. October 17th, 2009.



The Department of Psychiatry has a long tradition of research that focuses on the interface between psychiatry and medical illnesses. Methods include quantitative as sessment of various patient populations with specific attention to the personality characteristics common in patients who utilize somatic complaints as a proxy for psychosocial problems,a process termed somatization. The personality variable that captures the essence of this style is termed "alexithymia." Our re search investigates both convergent and divergent validation of the relationship between alexithymia and emotional intelli gence, which denotes an individual's abil ity to as certain emotional states in others, and understanding groups to effectively lead. Drs. Wise and Sheridan have focused on this area of research for over a decade, leading to the develop ment of the Emotional Intelligence Ques tionnaire, which is now validated in Japa nese, Turkish, and American subjects. Dr. Wise is also involved is the role of per sonality factors in Hepatitis C patients.

The initial study has been submitted for publication.

Both Drs Wise and Crone have contributed articles on the organization and education of psychiatric fellows in Psychosomatic Medicine. Review-ing research in the field of consultation psychiatry is also an ongoing endeavor. Dr. Wise is the editor of Advances in Psychosomatic Medicine. Both he and Dr. Crone are members of editorial boards of a variety of peer reviewed journals.

An additional area of research is the role of psychological factors in organ transplantation. Dr. Crone has edited a Psychiatric Clinics of North America. Her papers appear both in psychiatric journals and journals related to medical and surgical services.

A final area of research pertains to drug therapy for depression and anxiety. Dr. Wise has contributed several peer reviewed papers in this field.

Both Drs. Wise and Crone have presented their work at National Meetings such as the Academy of Psychosomatic Medicine and the Annual meeting of the American Psychiatric Association

BOOKS, BOOK CHAPTERS, AND JOURNAL ARTICLES

1. J Lackamp, C Osborne, T Wise. Paraphilic Disorders. Clinical Manual of Sexual Disorders. American Psychiatric Publishing, Inc. 2009.
2. L Worley, J Levenson, T Stern, S Epstein, J Rundell, T Wise. Core Competencies for Fellowship Training in Psychosomatic Medicine: A Collaborative Effort by APA Council on Psychosomatic Medicine, the ABPN Psychosomatic Committee, and The Academy of Psychosomatic Medicine. Psychosomatics 50:6, November-December 2009
3. T Wise. Psychological Factors Affecting Medical Conditions, a New Classification for DSM-V. Clinical Neuropsychiatry, 2009.

LECTURES AND FACULTY PRESENTATIONS TO NATIONAL/ INTERNATIONAL MEETINGS

1. The Worried Patient at Annual Med. Psych Conference at Baptist Hospital in Miami, Florida, March 2009
2. The Psychosomatic Perspective. International College of Psychoso matic Medicine. September 2009
3. Update on Psychosomatic Medicine. Annual Meeting of American College of Psychiatrists. April 2009
4. Mental Health in Primary Care. The World Federation of Mental Health and the Pan American Health Organization. October 8, 2009

The department of trauma services has been through some changes in 2009 and research is no exception. This group has maintained a commitment to research and expanded its horizons. Dr Margaret Griffen has taken over as Chief of Trauma Services and Dr Anne Rizzo has become the Director of Trauma Services Research. We have continued our interest in automotive safety and medical research with motor vehicle crashes through the Crash Injury Research and Engineering Network (CIREN). Several projects from this program have been accepted to national and international meetings for presentation in 2009-2010. Trauma services is in the process and reapplying for a grant for CIREN. Trauma Services has continued grant funding through several other sources and currently has seven grants through Inova. A HRSA grant for equipment for research support was concluded over the past year and multiple collaborative projects with researchers at George Mason University are underway.

A commitment to resident research education (SRRF) as well as many aspects of research in trauma and general surgery patient care is on going. The residents have had several abstracts accepted for presentation at regional, national and international meetings, the American College of Surgeons resident paper competition, the Society for University Surgeons, as examples. We are currently conducting a prospective clinical study involving ICU patients and procalcitonin and hope to have data completed for an abstract submission in 2010. The observation and collective review of a rare general surgical condition encountered several times in 2009 resulted in an abstract acceptance and travel to Australia for one resident.

Continued research in Trauma Services includes projects reviewing elderly trauma patients and the use of Coumadin, radiation exposure during trauma care, dosing of Fentanyl in the trauma patient. and metabolomics evaluation in the trauma patient. A collaboration with the Neurosurgery Orthopedics Division is expanding. A year of changes has brought challenges and gratitude for the efforts of all involved in the year's great successes.

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2. Michetti CP, Sakran JV, Grabowski JG, Thompson EV, Bennett K, Fakhry SM. Physical Examination is a Poor Screening Test for Abdominal-Pelvic Injury in Adult Blunt Trauma Patients. J Surg Res. 2009 Jun 6.
3. Vaziri K, Roland JC, Robinson LL, Reines HD, Fakhry SM. Extreme anemia in an injured Jehovah's Witness: a test of our understanding of the physiology of severe anemia and the threshold for blood transfusion. J Trauma. 2009 Jul;67(1):E11-3.
4. Holevar M, Dunham JC, Brautigan R, Clancy TV, Como JJ, Ebert JB, Griffen MM, Hoff WS, Kurek SJ Jr, Talbert SM, Tisherman SA. Practice management guidelines for timing of tracheostomy: the EAST practice management guidelines work group. J Trauma. 2009 Oct; 67(4):870-4.

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1. Rizzo A, Aldaghlas T,. Abdominopelvic Injuries in Lateral Motor Vehi cle Crashes with Side Airbags: Another Bag**?** Presented at the 8th Annual Public CIREN Meeting, Baltimore, MD, October 8, 2009.
2. Samir M Fakhry, MD*, Tayseer A Aldaghlas, MD, Linda Robinson, RN, MA, MS, HaniSeoudi, MD*, Anne Rizzo, MD*. Inova Regional Trauma Center. Computed Tomographic Angiography: False posi tives in the diagnosis of blunt cervical vascular injuries. Oral presen tation at the Sixty-eighth Annual Meeting of the American Association for the Surgery of Trauma, Pittsburgh, PA, October, 2009.
3. Samir M Fakhry MD*, Alaa Alhazmi MD, Tayseer Aldaghlas MD, Linda Robinson RN MA,MS, Kevin Dwyer MD*. Inova Regional Trauma Center. Impact of Chest Computerized Tomography for the Diagnosis of Pulmonary Embolus in Trauma Patients: A nine year experience at a Level One trauma center. Poster presentation at the Sixty-eighth Annual Meeting of the American Association for the Surgery of Trauma, Pittsburgh, PA, October, 2009.

EXAMPLES OF RESEARCH PRESENTATIONS BY MEMBERS OF RESEARCH TEAMS FROM

CENTER FOR LIVER DISEASES

AND

TRANSLATIONAL RESEARCH INSTITUTE

BETTY AND GUY BEATTY CENTER FOR INTEGRATED RESEARCH

INOVA HEALTH SYSTEM

Expression of Genes from JAK/STAT Pathway Are Associated with Factors Predicting Sustained Virologic Response to Treatment of Chronic Hepatitis C (CH-C)

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BACKGROUND

- Current standard treatment of CH-C with pegylated interferon-α and ribavirin (PEG-IFN+RBV) achieves sustained virologic response (SVR) in only half of the treated patients.
- Inability to achieve SVR has been strongly associated with a number of factors such as genotype 1, African American (AA) race, cirrhosis, high viral load (HVL), obesity, type 2 diabetes (T2D), age, and lack of early virologic response (EVR), suggesting innate systemic differences in host immune response to treatment.

AIM

- To asses the status of functional pathways based on genes differentially expressed in the pre-treatment peripheral blood mononuclear cells (PBMC) of CH-C patients that can be associated with negative predictors of response.

METHODS

- Pre-treatment blood samples were collected into PAXgene™ RNA tubes.
- CH-C patients scheduled to undergo treatment with PEG-IFN+RBV were included.
- Patients received a full course of PEG-IFN+RBV.
- EVR, and SVR rates were 76%, and 41% respectively.
- From pre-treatment PBMCs, total RNA was extracted, quantified and used for one step RT-PCR to profile 160 mRNAs.
- Expression of mRNAs were normalized with "housekeeping" genes.
- Differentially expressed genes were separated into up and down-regulated gene lists according to the presence or absence of a "predictive factor for SVR" and subjected to KEGG Pathway Painter that allows high-throughput visualization of the pathway-specific changes in expression profiles.
- Genes were consolidated into networks associated with these predictors of response.

RESULTS

Figure 1. JAK-STAT pathway upregulation. Upregulated genes are denoted in Red. Green panels indicate the cohorts that share upregulation in gene expression for given genes.

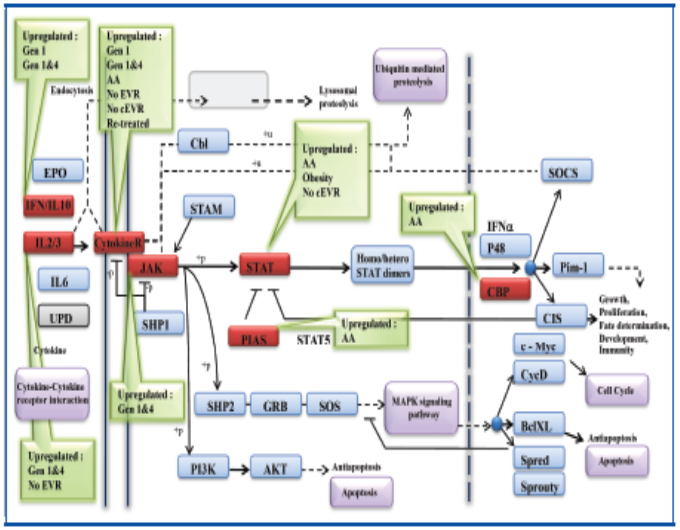


Figure 2. TGF-b pathway upregulation. Upregulated genes are denoted in Red. Green panels indicate the cohorts that share upregulation in gene expression for given genes

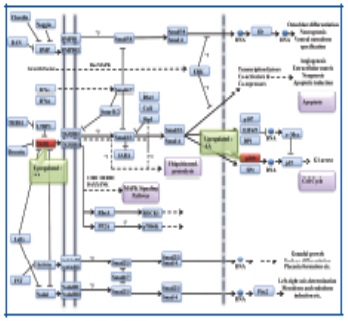
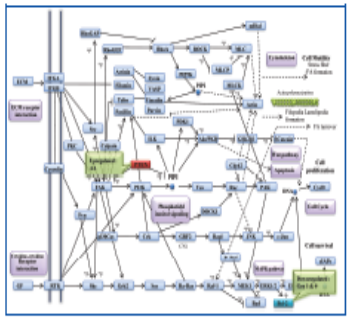


Figure 3. Focal adhesion pathway upregulation. Upregulated genes are denoted in Red, downregulated genes are denoted in blue. Green panels indicate the cohorts that share upregulation in gene expression for given genes.



*All Pathways adapted from KEGG

RESULTS

- Of 125 CH-C patients enrolled in the study, 68 had complete clinical and gene expression data.
- Pre-treatment gene expression for these CH-C patients show differential expression of 10 genes associated with HCV genotype 1, 46 genes with AA race, 5 genes with HVL, 6 genes with cirrhosis, 34 genes with obesity, 4 genes with T2D, 11 genes with older age, and 18 genes with lack of achieving EVR.
- Using KEGG Pathway Painter, these genes were mapped into their functional pathways.
- This analysis shows that genes associated with core components of the JAK/STAT pathway are pre-activated in CH-C patients who had negative predictors of SVR (Fig. 1).
- In addition TGF-β and Focal Adhesion pathways also contain differentially expressed genes associated with negative predictors of SVR (Fig. 1 & 2).

Table 1. Differentially Expressed Genes Between Cohorts

Cohorts	Number of Differentially Expressed Genes
HCV genotype 1	10
AA race	46
HVL	5
Cirrhosis	6
Obesity	34
T2D	4
Older Age	11
Lack ofAchievingEVR	18

CONCLUSIONS

- Pathway centered analysis of gene expression profiles from pre-treatment PMBC of CH-C patients points to the JAK-STAT signaling cascade as well as TGF-β pathway as potentially major pathogenetic components responsible for not achieving SVR.
- These pathways may delineate a link between host immune response and lack of achieving SVR.

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Proteomic Biomarkers Predicting Histologic Non-alcoholic Steatohepatitis and Fibrosis

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BACKGROUND

- Non-alcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease.
- NAFLD is the hepatic manifestation of metabolic syndrome and closely associated with visceral obesity.
- NAFLD ranges from simple steatosis to non-alcoholic steatohepatitis (NASH).
- Only the NASH subtype of NAFLD has been definitively shown to progress.

AIMS

- Develop non-invasive, diagnostic biomarkers for NASH and fibrosis based on changes in the signaling networks of white adipose tissue (WAT), which may participate in the pathogenesis of NASH and fibrosis.

METHODS

- Clinico-demographic data and WAT were collected from 213 patients who had undergone liver biopsy during bariatric surgery (Table 1).
- Patients were divided into training and validation cohorts (N = 144 and N = 69, respectively).
- All liver biopsies were interpreted by a single hepatopathologist.
- NASH was defined as steatosis, lobular inflammation and ballooning degeneration with or without Mallory bodies and/or fibrosis.
- Fibrosis was classified into 2 groups: 1) None to minimal fibrosis group: no or only mild portal or pericellular fibrosis, 2) Advanced fibrosis: moderate to severe fibrosis (Stage>2) group: at least moderate portal or pericellular fibrosis, bridging fibrosis or cirrhosis.
- Each cohort was categorized as 'with or without NASH', and 'with or without advanced (Stage>2) fibrosis'.
- From WAT, protein lysate was extracted and then used for RPA (Reverse Phase Protein Arrays) analysis, which quantitatively measured the relative phosphorylation of 24 specific signaling molecules.
- Regression models for predicting NASH and fibrosis (with these parameters used as dependent variables) were generated by step-wise bi-directional selection using data from the training cohort.
- Predictor variables used from modeling included: 1) clinical and demographic parameters only. 2) Phosphoproteomic profiles only, 3) a combination of clinical and phosphoproteomic parameters.

METHODS

- For resulting models, sensitivity, specificity, positive and negative predictive values, and AUCs were calculated using: 1) Only the training cohort validated by 10-CV method, 2) Only the training cohort validated using the blinded test cohort, 3) A combination of the training and test cohorts validated by 10-CV.

RESULTS

Table 1. Clinical data for patients with or without NASH, and with or without severe (Stage 2+) fibrosis.

Parameter	No NASH	NASH	No or Minimal Fibrosis	Advance Fibrosis
Sample Size, N	99	18	98	21
Age	43.80 ± 10.76	43.11 ± 11.70	43.81 ± 10.76	42.71 ± 11.54
Gender (1 = Female)	0.82	0.39	0.79	0.67
Race (1=White)	0.73	0.89	0.78	0.71
BMI	47.08 ± 8.96	48.11 ± 8.74	47.34 ± 8.92	46.81 ± 8.97
Waist, cm	134.48 ± 16.66	136.97 ± 16.65	134.44 ± 16.38	136.67 ± 17.96
Diabetes	0.22	0.35	0.23	0.29
Hyperlipidemia	0.41	0.38	0.44	0.25
Hypertension	0.63	0.71	0.62	0.71
Alcohol	0.63	0.59	0.63	0.57
Smoking	0.09	0.22	0.09	0.19
AST	22.14 ± 11.03	41.63 ± 32.29	22.06 ± 9.83	39.00 ± 32.75
ALT	28.49 ± 16.26	63.41 ± 32.12	29.82 ± 16.86	44.60 ± 32.86
Albumin	3.96 ± 0.49	4.25 ± 0.17	3.97 ± 0.48	4.12 ± 0.32
Total Bilirubin	0.46 ± 0.21	0.81 ± 0.27	0.46 ± 0.21	0.68 ± 0.27
White Blood Cell Count	7.97 ± 2.64	7.77 ± 1.89	7.79 ± 2.07	8.84 ± 3.74
Platelet Count	283.72 ± 62.72	244.78 ± 74.39	286.13 ± 63.17	246.52 ± 88.85
Hemoglobin	13.23 ± 1.40	14.32 ± 1.30	13.32 ± 1.38	13.76 ± 1.67
Glucose	105.31 ± 38.13	128.85 ± 48.49	107.32 ± 39.43	118.25 ± 44.83
Total Cholesterol	197.88 ± 44.42	200.00 ± 31.36	198.49 ± 44.76	196.89 ± 31.89
Triglycerides	176.03 ± 177.29	231.89 ± 110.75	188.78 ± 186.29	184.84 ± 88.07

- Overall, models predicting NASH were more accurate than those predicting fibrosis.
- All models were statistically significant ($p<0.05$); however they varied in the extent of their sensitivity, specificity, and other measures of accuracy.
- For NASH, the model based on phosphoproteins only performed the best, with an AUC = 0.772, sensitivity of 80% and specificity of 58%.
- This result was based on a training set that consisted of the training cohort only, and included the parameters: p4EBP1 S65 + peIF4G S1108 + pFAK Y397 + pFKHR S 256.
- The remaining models predicitng NASH (i.e. those based on clinical parameters only or clinical and proteomic data combined) also had good AUC values (0.711 and 0.722, respectively) but had lower sensitivity (40% and 50%, respectively) and higher specificity (84% and 87%, respectively).

RESULTS

Table 2. Results for modeling efforts to predict NASH using training cohort (N=144). All models reported were trained on the training cohort (only) and validated on the test cohort.

Parameters	p-value	Sensitivity (%)	Specificity (%)	+PV	-PV	Significant Parameters of the Model
Clinical	1.14E-07	40	84	25	91	ALT + AST + Race + Gender
Proteins	4.12E-02	80	58	32	92	P4EBP1.S65 + peIF4G.S1108 + pFAK.Y397 + pFKHR.S256
Clinical + Proteins	4.61E-08	60	87	38	92	pAKT.S473 + pcAb1.T735 + peIF4G.S1108 + peNOS.NOS.III.S116 + pFAK.Y397 + pFKHR.S256 + pPKA.C.T197 + pPKCd.T505 + Gender + ALT + pBAD.S136

RESULTS

- The best performing model for advanced fibrosis was based on phosphoproteins only, but had an AUC of just 0.524, 60% sensitivity, and 62% specificity.
- This model was based on data from the training cohort only and included the parameters: peIF4G S1108 + peNOS NOS III S116 + pIRS1 S612 + pPKA C T197.

Table 3. Results for modeling efforts to predict severe (Stage 2+) fibrosis using the training cohort (N=144). All models were trained on the training cohort (only) and validated on the test cohort.

Parameters	p-value	Sensitivity (%)	Specificity (%)	+PV	-PV	Significant Parameters of the Model
Clinical	4.22E-05	40	80	20	91	PLT + AST + Hypertension + Hyperlipidemia + Age
Proteins	3.73E-05	60	62	16	93	peIF4G.S1108 + peNOS.NOS.III.S116 + pIRS1.S612 + pPKA.C.T197
Clinical + Proteins	3.89E-07	60	16	6	75	Hyperlipidemia + AST + HGB + peIF4G.S1108 + peNOS.NOS.III.S116 + pIRS1.S612 + pp90RSK.S380 + pPKA.C.T197

- The models for advanced fibrosis generated from clinical data only or from clinical and proteomic data combined had similar AUC values (0.515 and 0.547, respectively), low sensitiviies (40% and 50%, respectively), and varied specifities (80% and 16%, respectively).
- Interestingly, the negative predictor values for all models except one (that predicting fibrosis based on clinical and proteomic data combined) were over 90%.

CONCLUSIONS

- Our results suggest that phosphoproteins could potentially be used in a clinical setting to identify patients with NASH.
- Furthermore, the results shed light on the biological pathways that may be involved in the pathogenesis of NASH.
- NASH was accurately predicted by a model based on four WAT phosphoproteins.
- Advanced fibrosis was not well predicted by WAT phosphoproteins, clinical data or both combined.

Differential Expression of miRNA in Patients with Non-Alcoholic Steatohepatitis

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BACKGROUND

- The role of obesity in the development of non-alcoholic fatty liver disease (NAFLD), and its more severe subtype, non-alcoholic steatohepatitis (NASH), is in part due to visceral adipose tissue producing an excess of cytokines and adipokines.
- MicroRNAs (miRNAs) are 21-23nt regulatory RNAs capable of suppressing expression (Figure 1).
- It is likely that the development of NASH is under direct or indirect miRNA control via the regulation of adipocytokines and other adipose genes.

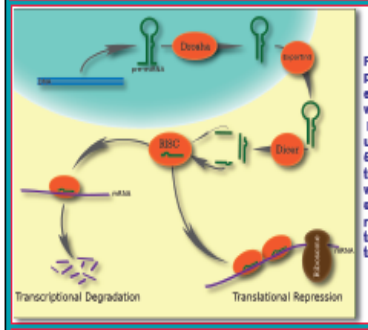

Figure 1: Pre-miRNA is initially processed by Drosha and then exported to the cytoplasm where it is further processed by Dicer. The miRNA strands unwind and either the 3' or the 5' strand may associate with the RISC complex. RISC loaded with the miRNA recognition sequence is then able to regulate expression by either translational inhibition or transcriptional degradation.

METHODS

- Visceral adipose tissue samples were collected from NAFLD patients during bariatric surgery and were snap frozen.
- All patients had liver biopsy-proven NAFLD and were divided into NASH (n=12) and non-NASH (n=12) groups, and by pericellular fibrosis (N=6) vs. no fibrosis (N=6) (Table 1).
- Both groups were similar in their clinical and demographic characteristics.
- Total RNA was extracted from the adipose tissue, reverse transcribed, and profiled using Taqman Human MicroRNA arrays (ABI) containing all known human miRNA species.
- Univariate Mann-Whitney comparisons and multivariate regression analysis were performed to compare patients with NASH to matched controls.

AIM

To profile miRNA expression in the visceral adipose tissue of NASH patients.

Table 1: Clinico-demographic and laboratory data

	NASH (N = 12)	Non-NASH NAFLD (N = 12)	P-Value	NASH with pericellular fibrosis (N = 6)	Non-NASH NAFLD (N = 6)	P-Value
Age, years	42.9 ± 13.6	49 ± 7	NS	52 ± 6.4	44.2 ± 12.1	NS
Female, %	75% (9)	75% (9)	NS	66.7% (4)	100% (6)	NS
Caucasian, %	83.3% (10)	83.3% (10)	NS	83.3% (5)	83.3% (5)	NS
Body mass index (BMI)	48.4 ± 7.3	45.4 ± 7.8	NS	46.3 ± 4.8	47.7 ± 10.0	NS
AST level, IU/L	25.2 ± 9.7	22.2 ± 8.2	NS	26.7 ± 11.5	19.8 ± 9.5	NS
ALT level, IU/L	33.3 ± 14.0	30.8 ± 12.1	NS	37.2 ± 18.4	29.2 ± 13.0	NS
AST/ALT	0.79 ± 0.18	0.75 ± 0.20	NS	0.76 ± 0.15	0.70 ± 0.21	NS
Type 2 DM, %	50% (6)	50% (6)	NS	50(3)	66.67(4)	NS
Fasting serum triglyceride, mg/dL	178.0 ± 112.2	161.8 ± 56.8	NS	227.7 ± 129.9	163.8 ± 80.4	NS
Fasting serum cholesterol, mg/dL	185.3 ± 70.4	195.4 ± 23.0	NS	223.0 ± 46.1	196.0 ± 12.5	NS
Fasting serum glucose, mg/dl	113.6 ± 52.0	111.8 ± 26.9	NS	130.8 ± 49.5	110.4 ± 10.8	NS

Table 2: miRNA Regulated Adipocytokines

TNFSF14	TNFSF12	TNFSF11	TNF-α	IL15RA	IL6	CD40LG	*LEP
hsa-miR-885-5p	hsa-miR-768-3p	hsa-miR-565	hsa-miR-875-5p	hsa-miR-135a	hsa-miR-643	hsa-miR-582-5p	hsa-miR-875-5p
hsa-miR-629	hsa-miR-573	hsa-miR-543	hsa-miR-519b-3p	hsa-miR-330-3p	hsa-miR-576-3p	hsa-miR-522	
hsa-miR-574-3p	hsa-miR-550	hsa-miR-532-3p	hsa-miR-337-3p	hsa-miR-502-5p	hsa-miR-574-3p	hsa-miR-135a	
hsa-miR-519d	hsa-miR-516a-3p	hsa-miR-485-3p	hsa-miR-149	hsa-miR-516a-3p	hsa-miR-522	hsa-miR-133b	
hsa-miR-502-3p	hsa-miR-502-5p	hsa-miR-337-3p	hsa-miR-125b	hsa-miR-517a	hsa-miR-149		
hsa-miR-339-3p				hsa-miR-517c	hsa-miR-146b-3p		
hsa-miR-331-3p				hsa-miR-622	hsa-miR-132		
hsa-miR-197				hsa-miR-886-3p			
hsa-miR-150				hsa-miR-923			
hsa-miR-125b				hsa-miR-941			
hsa-miR-125a-3p							

Table 2: Partial list of Notable Soluble Molecules Targeted by a significant number of differentially expressed miRNA: * Although LEP is only targeted by a single differentially expressed miRNA it is predicted to only targeted by a total of 6 miRNA species.

Figure 2: miRNA and Androgen Signalling

Figure 2: In addition to the 3 miRNA species intergenic to elements of androgen signaling, several differentially expressed miRNA either directly or indirectly influence androgen signaling strongly implying a more important roll for this pathway than previously apreciated

Figure 3: Indirect Regulation of Adipocytokines

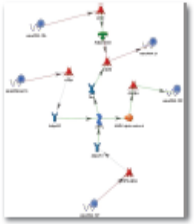

Figure 3: Molecules under the direct regulation of relevant miRNA species control the expression of adipocytokine signaling components

RESULTS

- A total of 113 species of miRNA were differentially expressed in the visceral adipose of NASH patients compared to those with non-NASH type of NAFLD (|Fold Change| > 1.7, P<0.05).
- 7 differentially expressed miRNA species passed stringent multiple test correction (hsa-miR-132, hsa-miR-150, hsa-miR-433, hsa-miR-28-3p, hsa-miR-511, hsa-miR-517a, hsa-miR-671).
- Thirty five species of miRNA were differentially expressed in the visceral adipose of NASH patients with pericellar fibrosis versus those with non-NASH, two of which passed multiple test correction (hsa-miR-197 and hsa-miR-99).
- Additionally, the expression of two miRNA species were specifically altered only in the subgroup of patients with both NASH and pericellular fibrosis, but were not changed when entire NASH non-NASH NAFLD cohorts were compared (hsa-miR-146b-3p and hsa-miR-149).

DISCUSSION

- Differentially expressed miRNA species such as hsa-miR-99a and hsa-miR-132 have been previously shown to negatively correlate in the visceral adipose with macrophage infiltration, visceral area, LDL, total cholesterol, free fatty acid levels, and IL6 concentration
- Three miRNA species, hsa-miR-7, hsa-miR-26a, and hsa-miR-604 are all intergenic to genes associated with androgen hormone signaling (SVIL, CTDSP2, and HNRNPK). In addition several androgen hormone signaling components are under direct or indirect miRNA regulation (Figure 2).
- Several direct targets of miRNA regulation, as predicted by miRanda, are soluble molecules that have been shown previously to be expressed by visceral adipose tissue in connection with NASH (Table 2).
- Other significant adipokine signaling, such as adiponectin and adiponecten receptor expression, shows a strong likelihood of indirect regulation by miRNA.

CONCLUSIONS

- Differential expression of miRNA in the visceral adipose may elucidate pathways important for the pathogenesis of NASH. Furthermore, these data can help develop new targets for treatment of NASH.

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A Panel of Gene Expression Biomarkers Predicting Sustained Virologic Response (SVR) in Chronic Hepatitis C Patients (CH-C) Treated with Pegylated Interferon Alpha and

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BACKGROUND

- Chronic hepatitis C (HCV) is the most common cause of chronic liver disease, hepatocellular carcinoma, and the most common indication for liver translantation. Pegylated interferon-alfa based regimens comprise the standard treatment for chronic hepatitis C.
- In general, 47-54% of patients who have never been previously treated (treatment-naive) acheive sustained virolic response (SVR) with this regimen. This rate is lowest for patients with HCV genotype 1 (HCV-G1, ~40%) and highest for patients infected with HCV genotype 2 (HCV-G2, 85-90%).
- The determinants of successful treatment include viral factors (HCV genotype, pre-treatment viral load, viral quasispecies, host factors (obesity, cirrhosis, ethnic background, serum cytokine levels), and treatment factors (prescribing the adequate course of treatment, adherence to the course of treatment, optimal management of side effects).
- In addition to these factors, viral response pattern early during antiviral therapy can predict a response or a lack thereof.

AIM

- The aim of this study was to determine the association between gene expression profiles of 154 human RNA transcripts in peripheral blood mononuclear cells of patients receiving PEG-IFN and RBV and relate these expression profiles to response to the treatment.
- This is part of an on-going effort to develop a panel of gene expression biomarkers that can accurately predict SVR early during the first few weeks of antiviral therapy.

METHODS

- Gene expression comparisons were performed for the expression levels of each gene quantified during each of the five visits (pre-treatment visit, and days 1, 7, 28 and 56 of the treatment) by Mann-Whitney tests.
- Total RNA extracts were obtained at different time points, quantified and used for one step RT-PCR to profile 154 mRNAs reflecting expression of 153 human genes that belong to various IFN-inducible and immune response-related pathways, along with a number of "housekeeping" genes.
- RT-PCR was performed in 384-well format with a duplicate of each 15-ul reaction using Prism (R) 7900HT Sequence Detection System mRNA expression levels were normalized by using six housekeeping genes and a reference RNA. The final [two change signs] CT values of 148 mRNAs were used for statistical analyses.
- Blood samples of mRNA profiling were collected in three PAXgene (TM) RNA blood tubes (PreAnalytiX) prior to the initiation of treatment as well as on day 1, day 7, day 28 and day 56 after the initiation of treatment.
- To assess whether the pattern of gene expression in peripheral blood cells is cater to predicting a sustained response to PEG-IFN+RBV treatment we performed a multiple regression analysis with stepwise (bi-directional) selection of variables for all the cohorts and all the comparisons in each cohort and visit day.
- The sensitivity, specificity, and area under the ROC-curve (AUC) with 95% confidence intervals (CIs) were calculated for each model. The final [two change signs] CT values of 148 mRNAs were used for statistical analyses. All predictive models were cross-validated using the leave-one-out (LOO) method.

RESULTS

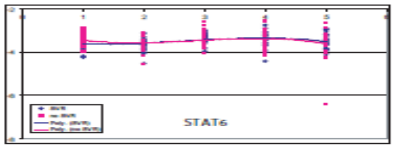
- Of the entire cohort, 51% were naive and 49% were non-responders to combination therapy. After a standard course of PEG-IFN & RBV, 45% achieved SVR.

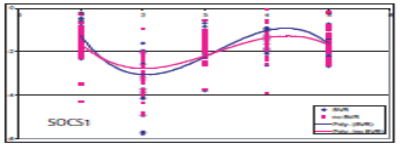
Table 1. Characteristics of treatment naive and previously treated patients

Characteristics	All HCV patients
Number of Patients	55
Sex - Male	36 (61%)
Age	48.2 ± 6.9
Race, Caucasians	39 (66%)
HCV genotype 1	44 (75%)
Pretreatment ALT	101 ± 70
Pretreatment HCV RNA (IU/mL)	4,453,576 ± 5,337,476
Sustained Virologic Response (Overall)	27/59 (46%)
Sustained Virologic Response (Genotype 1)	17/44 (39%)
Sustained Virologic Response (Non-Genotype 1)	10/15 (67%)

- Using the pre-treatment blood samples, SVR could be predicted by the gene expression levels of STAT6 and SOCS1 [Model p=value <0.002, AUC = 0.718 (CI: 0.671 - 0.906), Sensitivity = 0.708, Specificity = 0.840].

Graphs 1&2: Expression Patterns of STAT6 and SOCS1 genes during antiviral treament by RT-PCR using the combined cohort of subjects.





- After 24 hours of treatment, SVR could be predicted by the gene expression levels of LIPA, NMI, RHOC, and BCL2 [Model p=value <0.0004, AUC = 0.808 (CI: 0.671 - 0.906), Sensitivity = 0.708, Specificity = 0.840].
- Interestingly, the pre-treatment models predicting SVR were based mostly at expression levels of various intracellular signaling molecules (see Tables), while both at early and late time points of the treatment SVR was predicted by the expression of the effector genes.
- Performance of the predictive models improved toward later stages of treatment. Before treatment, AUC of LOO validated model was 0.718, while at day 56 similarly calculated AUC was 0.853. Latter models were based on gene expression of IRF5 and PSME2.

CONCLUSION

- The complex patterns of gene expression in lymphocytes taken from the peripheral blood of the patients with HCV infection obtained in the pre-treatment period or shortly after the initiation of treatment could be reduced to small gene subsets allowing for the prediction of SVR.
- After proper validation, these gene sets may provide the basis for the non-invasive diagnostic biomarker that can determine early if a patient treated with PEG-IFN and RBV is likely to achieve SVR.
- By focusing the full course of treatment on only those patients who have the highest likelihood of achieving SVR, clinicians could potentially reduce side effects and costs associated with these treatment regimens and provide a "personalized approach" to the treatment of patients with chronic hepatitis C.

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Gene Expression Associated with Advanced Fibrosis in Patients with Chronic Hepatitis C (CH-C)

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BACKGROUND

- Chronic hepatitis C (HCV) is the most common cause of chronic liver disease, hepatocellular carcinoma, and the most common indication for liver translantation.
- CH-C patients with advanced fibrosis are at risk for development complications such as hepatocellular carcinoma and hepatic decompensation.
- Factors associated with the occurence of severe liver fibrosis in CH-C patients remain poorly understood. Expression of the genes in peripheral blood lymphocytes may reflect the severity of liver fibrosis.

AIM

- The aim of this study was to determine the association between gene expression profiles of 154 human RNA transcripts in peripheral blood mononuclear cells of patients on various stages of treatment and relate these expressions profiles to the presence of the liver fibrosis.
- This is part of an on-going effort to develop a panel of gene expression biomarkers that can accurately predict the extent of the chronic liver disease without the need for liver biobsy.

METHODS

- Blood samples for mRNA profiling were collected in three PAXgene(TM) RNA blood tubes (PreAnalytiX) prior to the initiation of treatment.
- Total RNA extracts were obtained at different time points, quantified, and used for one step RT-PCR to profile 154 mRNAs reflecting expression of 153 human genes that belong to various IRN-inducible and immune response related pathways along with a number of "housekeeping" genes.
- RT-PCR was performed in 384-well format with a duplicate of each 15-ul reaction using Prism (R) 7900HT Sequence Detection System mRNA expression levels were normalized by using six housekeeping genes and a reference RNA. The final [two change signs] CT values of 148 mRNAs were used for statistical analyses.
- Gene expresswion comparisons were performed for the expression levels of each gene by Mann-Whitney tests.
- To assess whether the pattern of gene expression in peripheral blood cells is cater to predicting fibrosis, we performed a multiple regression analysis with stepwise (bio-directional) selection of variables for all the cohorts and all the comparisons in each cohort and visit day.
- The sensitivity, specificity, and area under the ROC-curve (AUC) with 95% confidence intervals (CIs) were calculated for the model.

RESULTS

- 57 CH-C patients who were not recieving any HCV treatment were included. According to the liver biobsies, 30 patinets had advanced

Table 1. Demographics and Clinical Characteristics of CH-C Patients

Characteristics	Fibrosis	No Fibrosis	□	p-value
Number of Patients	30	27	57	NS
Sex - Male	19 (63%)	16 (59%)	35 (61%)	NS
Age	49.3 ± 7.6	46.9 ± 4.6	48.2 ± 6.4	NS
Race, Caucasians	20 (67%)	18 (67%)	38 (67%)	NS
BMI	28.9 ± 5.7	29.1 ± 5.7	29.0 ± 5.6	NS
HCV genotype 1	20 (67%)	22 (81%)	42 (74%)	NS
Pretreatment ALT	118.0 ± 79.0	78.2 ± 51.0	99.3 ± 69.9	0.023
Pretreatment HCV RNA (IU/mL)	3,643,933 ± 4,677,103	4,429,481 ± 5,363,068	4,017,088 ± 4,983,784	NS
Sustained Virologic Response (Overall)	14 / 30 (47%)	11/ 27 (41%)	25/57 (44%)	NS
Sustained Virologic Response (Genotype 1)	8/20 (40%)	8/22 (36%)	16/42 (38%)	NS
Sustained Virologic Response (Non-Genotype 1)	6/10 (60%)	3/5 (60%)	9/15 (60%)	NS

- Levels of expression for genes IFITM2, GBP2, PSMB8, PSME1, PSME2, IL15, NUBI were significantly decreased in CH-C patients with advanced fibrosis (p-value <0.05)

Table 2. Genes with Significant Differential Expression between CH-C patients with fibrosis and CH-C patients without fibrosis.

Gene	Gene function	Expression in Fibrosis, mean +/-SD	Expression in No Fibrosis, mean +/-SD	P-value
IFITM2	Interferon induced transmembrane protein 2 (1-8D)	-1.35+/- 0.50	-1.28+/- 1.83	0.033
GBP2	Inducible by interferon. Binds guanine nucleotides (GMP, GDP, and GTP)	-8.88+/- 0.48	-8.38 +/-0.73	0.034
PSMB8	A member of the proteasome B-type family. Expression of PSMB8 is induced by gamma interferon. Replaces catalytic subunit 3 (proteasome beta 5 subunit) in the immunoproteasome.	-3.07 +/- 0.33	-2.88+/-0.44	0.043
PSME1	Regulator part of the immunoproteasome that processes class I MHC peptides. PSME1 gene encodes the alpha subunit of the 11S regulator, one of the two 11S subunits that is induced by gamma-interferon.	-1.43 +/- 0.28	-1.78 +/- 0.41	0.006
PSME2	Regulator part of the immunoproteasome that processes class I MHC peptides. PSME2 gene encodes the beta subunit of the 11S regulator, one of the two 11S subunits that is induced by gamma-interferon.	-1.34 +/- 0.60	-1.11 +/- 0.38	0.034
IL15	Regulates T and natural killer cell activation and proliferation. Shares many biological activities with IL2. The number of CD8+ memory cells is shown to be controlled by a balance between this cytokine and IL2. Induces the activation of JAK kinases, STAT3, STAT5, and STAT6. Induce the expression of anti-apoptotic BCL2L1/BCL-X(L).	-2.73 +/- 0.49	-2.37 +/- 0.64	0.004
NUBI	Facilitator of proteasome degradation. Interacts with and negatively regulates NEDD8, a ubiquitin-like protein that covalently conjugates to cullin family members.	-2.04 +/- 0.48	-1.80 +/- 0.44	0.027

- Interestingly, 4 out of 7 of these mMRNAs encode for various parts of immunoproteasome that processes class I MHC peptides (NUBI, PSMB*, PSME1, and PSME2) emphasizing the role of antigenic response in the development of hepatic fibrosis in CHI-C.
- Additionally, in multivariate analysis, advanced fibrosis could be predicted by IL15 gene expression in the peripheral blood lymphocytes [Model p-value <0.0032, AUC = 0.723 (95%CI: 0.589 - 0.834)].

CONCLUSION

- A gene expression biomarker panel can predict advanced fibrosis in CH-C patients. After further validation, this biomarker can become useful in the management of patients with CH-C.

OBESITY RESEARCH

BETTY AND GUY BEATTY CENTER FOR INTEGRATED RESEARCH

INOVA HEALTH SYSTEM

Profiling and Validation of Reference Genes in the Visceral Adipose Tissue (VAT)

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3. Center for Liver Diseases, Inova Fairfax Hospital, Falls Church, VA, USA.

BACKGROUND

- VAT plays a central role in the pathogenesis of obesity and metabolic syndrome.
- There is a need for better understanding the molecular circuitry governing VAT functions.
- This warrants a thorough investigation of the VAT transcriptome.
- The qPCR method is a highly sensitive and specific technique for the measurement of gene expression; however, it is intrinsically dependent on the accurate selection of reference genes for data normalization.

AIM

- Our aim was to evaluate the most common reference genes and determine their ability to serve as reference genes for qPCR profiling of human VAT.

METHODS

- VAT samples were collected from obese patients (n=5) and lean patients undergoing abdominal surgeries (N=4).
- Total mRNA was extracted and used to determine the expression levels of 8 commonly used reference genes, encoding for:
  - 18S RNA, beta-2-microglobulin(B2M),
  - glyceraldehyde-3-phosphate dehydrogenase (GAPDH),
  - hydroxymethyl-bilane synthase(HMBS),
  - hypoxanthine phosphoribosyl-transferase 1(HPRT1),
  - ubiquitin C(UBC),
  - beta-actin(ACTB),
  - tyrosine 3-monooxygenase/tryptophan 5- monooxygenase activation protein,
  - zeta polypeptide(YWHAZ)
  - RNA polymerase II polypeptide(RP II).
- The qPCR experiments were performed in triplicates.
- Data were analyzed and compared using three publically available reference gene validation tools:GeNorm, BestKeeper, and NormFinder.

RESULTS

Figure 1. BestKeeper softtware algorithm and GeNorm analysis

GeNorm

$$V_{jk} = st.dev\,(A_{jk})$$

$$M_j = \frac{\sum_{k=1}^{n} V_{jk}}{n-1}$$

GeNorm Analysis

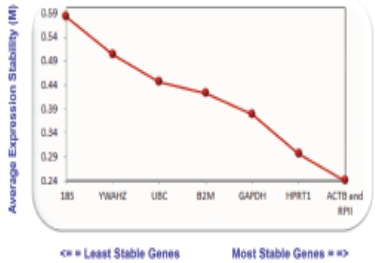


Figure 2. BestKeeper algorithm and analysis

BestKeeper

$$BestKeeper\ Index = \sqrt[n]{CP_1 \times CP_2 \times CP_3 \times \ldots\ldots \times CP_n}$$

BestKeeper Analysis

Regression Analysis	ACTB	RPII	HPRT1	GAPDH
r	0.981	0.975	0.966	0.915
ρ	0.001	0.001	0.001	0.001

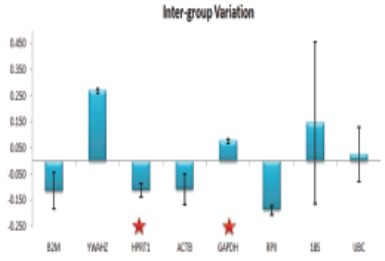
Figure 3. NormFinder algorithm and analysis

NormFinder Software

$$y_{ijg} = \alpha_{ig} + \beta_{ij} + \varepsilon_{ijg}$$

$$\rho_{ig} = \frac{\hat{\gamma}^2 |d_{ij}|}{\hat{\gamma}^2 + \hat{\sigma}^2_{ig}/n_g} + \sqrt{\hat{\sigma}^2_{ig}/n_g + \frac{\hat{\gamma}^2 \hat{\sigma}^2_{ig}/n_g}{\hat{\gamma}^2 + \hat{\sigma}^2_{ig}/n_g}}$$

NormFinder Analysis



RESULTS

- Despite the differences in the algorithms used for each software:
  - ACTB (expression stability coefficient M=0.239)
  - RP II (M=0.239) followed by GAPDH(M= 0.378)
  - HPRT1(M= 0.295) were ranked highest by all three analysis software.
- On the other hand, 18S RNA, most commonly used as a qPCR reference gene, was shown to be highly variable in VAT.

Table 1. Differentially Expressed Genes Between Cohorts

Gene Names	GeNorm (M)	Best Keeper (r)	NormFinder (r)
ACTB	0.239	0.981	0.222
RPII	0.239	0.975	0.244
HPRT1	0.295	0.966	0.193
GAPDH	0.378	0.915	0.130
B2M	0.421		0.236
UBC	0.446		0.207
YWAHZ	0.502		0.306
18S	0.581		0.344

CONCLUSIONS

- This study shows the variability in gene expression of commonly used housekeeping genes and suggest ACTB and RP II genes as the recommended reference genes for studies of VAT.

Differential Gene Expression Profiling of Brown Adipose Tissue (BAT) Specific Genes in Visceral Adipose Tissue of Lean and Obese Individuals

INOVA FAIRFAX HOSPITAL

GEORGE MASON UNIVERSITY

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BACKGROUND

- The epidemic of obesity and its associated disorders in the US are expected to become a major cause of mortality, morbidity and resource utilization.
- Significant efforts have been made to understand the properties and functions of adipose tissue and its contribution to fat metabolism.
- BAT is predominantly seen in newborns and is associated with thermogenesis.
- Recently, a role for BAT in adults and their body weight homeostasis has been suggested.

AIM

- The aim of this study was to detect and to quantify expression levels of BAT specific genes in the visceral adipose of lean and obese patients.

METHODS

- Visceral adipose tissue samples were collected from very obese patients undergoing bariatric surgery (n =5) and lean patients undergoing non-bariatric abdominal surgeries (N=4).
- Each specimen was snap frozen in liquid nitrogen and stored at -80.
- From each sample, total mRNA was extracted; the expression levels of the following BAT related genes were evaluated in triplicates by qPCR.

UCP1	PGC-1a
PPARD	Twist-1
PRDM16	SIRT 2
SIRT 3	NAMPT

- Univariate Mann-Whitney comparisons were performed.

RESULTS

Figure 1. Relationship between prevelence of visceral adipose tissue, brown adipose tissue and obesity.

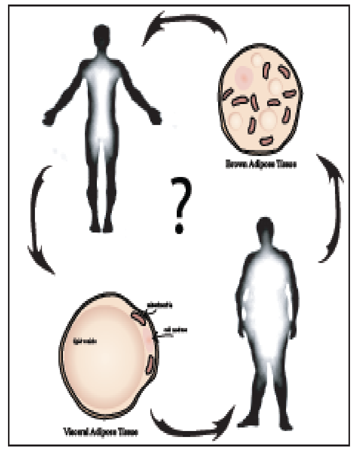
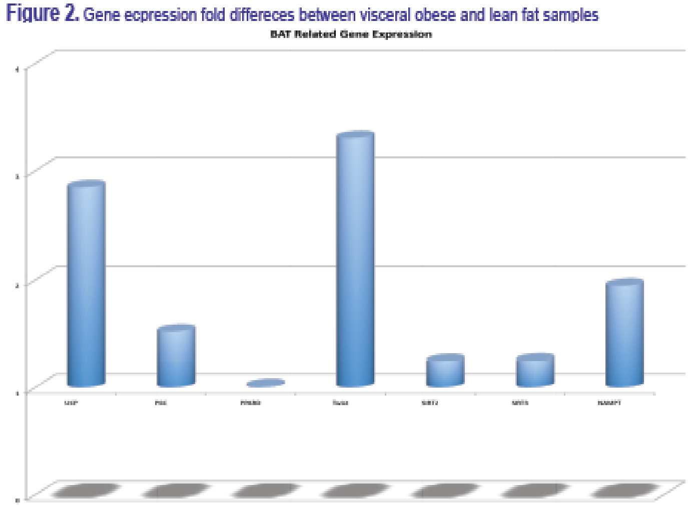


Figure 2. Gene ecpression fold differeces between visceral obese and lean fat samples



RESULTS

- The expression levels of UCP, PGC, Twist and SIRT3 were significantly higher (P < 0.015) in adipose samples of lean patients as compared to that of obese patients.
- Similar trends were observed for the visfatin encoding gene NAMPT (fold difference = 1.95, p= 0.029).
- However, there were no statistically significant differences in the expression levels of PPARD and SIRT2 in visceral adipose samples of lean and obese subjects.

Table 1. Gene expression fold changes as compared to visceral obese

Norm Exp level from GeNorm							
	UCP1	PGC	PPARD	Twist	SIRT2	SIRT3	NAMPT
Ob	[illegible]	1	1	1	1	1	1
	[illegible]	1	1	[illegible]	1	1	[illegible]
	[illegible]	[illegible]	1	[illegible]	1	[illegible]	[illegible]
	[illegible]	[illegible]	1	[illegible]	1	1	[illegible]
Ln	1.89306	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	1.89306	[illegible]	[illegible]	1.89306	[illegible]	[illegible]	[illegible]
	1.481751646	1.481751646	[illegible]	1.481751646	[illegible]	1.481751646	1.481751646
	1.189451982	1.189451982	[illegible]	1.189451982	[illegible]	[illegible]	1.189451982
Fold change	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
p-Value	[illegible]	[illegible]	0.557143	[illegible]	0.557143	[illegible]	[illegible]

* Significant values in RED

** Blue indicates obese greater than lean

CONCLUSIONS

- **This pilot study points to an increased expression of BAT-related genes in lean visceral adipose as compared to obese visceral adipose.**
- **This data suggest a higher level of BAT in the visceral adipose tissue of lean individuals, potentially indicating a relationship between BAT and obesity.**
- **After confirmation in a larger study, therapeutic strategies can be developed to target BAT and provide an alternative for treatment of obesity.**

INOVA FAIRFAX HOSPITAL

The Impact of Laparoscopic Bariatric Surgery on Components of Metabolic Syndrome

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BACKGROUND

- Metabolic Syndrome (MS) and Non-Alcoholic Fatty Liver Disease (NAFLD) are commonly found in morbidly obese patients undergoing bariatric surgery.

AIM

- This study aims to assess the impact of bariatric surgery on the resolution of MS and NAFLD.

METHODS

- Two hundred and sixty three patients who underwent bariatric surgery were included.
- Of these, two hundred and thirty six had at least one follow-up.
- Clinical, demographic and histologic data were available at the time of surgery and for follow-up after surgery.
- MS was defined according to ATP III (The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults).

RESULTS

- Clinical, demographic and laboratory data for the entire cohort are submitted in Table 1.
- Patients underwent restrictive, malaborptive or combination surgical procedures.
- Of the entire cohort, 27.0% underwent malabsorptive surgery, 57.0% underwent restrictive surgery, and 16.0% underwent combination restrictive-malabsorptive surgery.

RESULTS

- The majority (98.5%) of the surgical procedures were performed laproscopically.
- Mean weight loss after surgery was 33.7 +/- 20.1 kg after malaborptive surgery (follow-up period 306 +/- 290 days) and 28.3 +/- 14.1 kg after combination surgery (follow-up period 281 +/-239 days).

Table 1: Baseline Demographic and Clinical Characteristics

Characteristics		Categorical variables: Percent, % Numeric variables: Mean ± SD			
		All patients	Restrictive	Malabsorptive	Combination
Age (years)		44.0 ± 11.5	44.0 ± 11.0	46.1 ± 10.8	41.8 ± 12.2
Male, %		21.8	27.0	26.5	8.2
Diabetes, %		30.1	30.1	25.4	35.4
Metabolic Syndrome, %		39.2	41.3	38.1	31.7
Components of Metabolic Syndrome (ATP III criteria), %	Waist circumference	100.0	100.0	100.0	100.0
	Fasting triglycerides	41.5	38.6	43.4	48.3
	HDL cholesterol	44.9	47.3	38.7	52.4
	Blood pressure	59.6	64.4	56.2	43.2
	Fasting glucose	32.7	34.8	34.0	23.1
BMI		48.7 ± 9.4	50.2 ± 11.1	47.2 ± 6.7	45.9 ± 5.7
WGHT (kg)		137.7 ± 31.5	142.4 ± 36.6	136.9 ± 22.5	124.9 ± 21.1
WAIST (cm)		139.0 ± 20.4	140.1 ± 22.0	140.1 ± 16.8	134.7 ± 17.8
Fasting triglycerides (mg/dL)		170.8 ± 100.4	172.3 ± 105.4	175.0 ± 107.7	150.8 ± 86.7
HDL cholesterol (mg/dL)		48.0 ± 13.3	47.5 ± 13.8	49.9 ± 12.8	46.5 ± 12.1
Fasting glucose (mg/dL)		113.3 ± 45.9	116.9 ± 50.1	107.1 ± 30.1	111.8 ± 54.3
ALT		30.0 ± 20.1	31.1 ± 22.0	29.8 ± 17.6	26.4 ± 16.4
AST		23.5 ± 14.9	23.3 ± 15.8	24.8 ± 14.9	21.8 ± 11.6

RESULTS

- The amount of weight loss post-surgery was not significantly different among the three types of bariatric surgical procedures (p=.352).
- Regardless of the type of bariatric surgery, siginificant improvements were noted in:
  - DM (p-values from <0.0001 to 0.0005)
  - MS (p-values from <0.0001 to 0.01)
  - Waist circumference (p-values <0.0001)
  - BMI (p-values <0.0001)
  - Fasting serum triglycerides (p-value <0.0001 to 0.001)
  - Fasting serum glucose (p<0.0001, except for the combination surgery)
- Additionally, a significant improvement in ALT/AST ratio (p=.0002) was noted only in those who underwent restrictive surgery.
- Multivariate analysis showed that patients who underwent a malabsorptive bariatric procedure experienced greater percent weight loss of excess body weight (PWLEBW) than patients who underwent restrictive procedure (p-value = 0.0451).
- PWLEBW increased with longer post-operative follow-up (p-value <0.0001).

CONCLUSIONS

- Weight loss after bariatric surgery is associated with a significant improvement in Metabolic Syndrome (MS) and factors associated with Non-Alcoholic Fatty Liver Disease (NAFLD).

OUTCOMES RESEARCH PROGRAM

BETTY AND GUY BEATTY CENTER FOR INTEGRATED RESEARCH

INOVA HEALTH SYSTEM

Relationship Between Chronic Sleep Restriction and Health-Related Quality of Life

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Background

- Sleep is thought to be closely related to the regulation of emotional and physical well-being.
- In the general population, chronic sleep restriction is a very common behavior that has been rarely studied for its effect on emotional and physical well-being.
- Experimental sleep deprivation studies have identified a relationship between lack of sleep and emotional/physical well-being.
- However, these studies usually have severely restricted sleep.
- The relationship between less sleep and emotional/physical well-being in the general population has not been as thoroughly investigated.

Aim

- Examine the relationship between average number of hours slept per night and emotional and physical well-being, as measured by health-related quality of life (HRQL).

Methods

- Participants were recruited from a sample of blood donors in a community setting.
- These individuals filled in questionnaires assessing the average number of hours of sleep per night and a validated measure of HRQL that assesses overall HRQL score and the following domains:
  - Emotional Functioning (EF),
  - Systemic Symptoms (SS)
  - Worry (WO)
  - Activity (AC)

Results

- One hundred Blood donors (age: 52 ± 15 years; 66% male) were recruited in a community setting.
- In this sample, the individuals slept an average of 7.0 ± 1.1 hours per night.
- Statistically significant Spearman's correlations were present between number of hours of sleep and EF (rs=0.36; p<0.001), SS (rs=0.23; p=0.02), WO (rs=0.31; p=0.002), and overall HRQL score (rs=0.28; p=0.005).
- The relationships indicated that the lower the number of hours of sleep, the most impaired scores on the CLDQ.
- The correlations remained statistically significant after controlling for age, gender, and body-mass index.

Table 1. Demographics and HRQL

	Mean, SD
Total # Subjects (N)	100
Age	52.2 ± 14.8
Gender (% male)	66%
Body Mass Index (BMI)	27.7 ± 5.1
Sleep (Hours per night)	7.0 ± 1.1
Systemic Symptoms (SS)	5.8 ± 0.9
Emotional Functioning (EF)	6.1 ± 0.6
Activity Score (AS)	6.7 ± 0.5
Worry (WO)	6.8 ± 0.2
Total HRQL Score	6.3 ± 0.4

Results

Table 2. Sleep & HRQL Correlation Matrix

	Spearman Correlations	P-value
Systemic Symptoms (SS)	0.23	0.02
Emotional Functioning (EF)	0.36	<0.001
Activity Score (AS)	0.03	0.79
Worry (WO)	0.31	0.002
Total HRQL Score	0.28	0.005

Table 3. Adjusted Sleep & HRQL Correlation Matrix

	Spearman Correlations	P-value
Systemic Symptoms (SS)	0.23	0.02
Emotional Functioning (EF)	0.43	<0.001
Activity Score (AS)	0.07	0.49
Worry (WO)	0.33	0.001
Total HRQL Score	0.32	0.001

Conclusions

- This investigation demonstrates that a relationship exists between the average number of hours slept per night and HRQL (especially EF).
- The participants in the current investigation may not have adequate personal resources, including sufficient sleep, to self-regulate their EF.

Activity Level in Patients Undergoing Bariatric Surgery

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Background

- Various types of bariatric surgery are being used for management of morbid obesity.
- Impact of bariatric surgery on the activity level of patients has not been fully studied.

Aim

- To assess the impact of weight loss after surgery on patients' activity level.

Methods

- Patients who had undergone bariatric surgery for whom baseline and follow-up clinical data were selected.
- Each patient was sent a copy of the Human Activity Profile, a well-validated and reliable self-report measure of activity level that measures maximal activity level (MAS), and adjusted activity level (AAS)
- MAS score measures the maximal level of activity an individual can accomplish.
- AAS measures the level of activty engaged on a daily basis.
- Bariatric surgery patients were compared to BMI-matched controls without bariatric surgery.
- Comparisons between groups were made using Kruskal-wallis, Wilcoxon two-sample tests, Pearson correlations, and chi-square homogeneity tests.

Results

- A total of 84 patients were included in this study (72.1% female, age 51.6 ± 10.7, 92.9% white, and 4.7% African American).
- All cases and controls had liver biopsies showing non-alcoholic fatty liver disease (NAFLD).
- Of the entire cohort, 53 patients had undergone bariatric surgery (12 restrictive, 8 malabsorptive, 33 combined restrictive-malabsorptive therapy).
- For the bariatric surgery group, pre-surgical body mass index (BMI) was 47.1± 6.1.
- After 2.8 ± 1.4 years of follow-up, their post-surgery BMI after weight loss was reduced to 30.9 ± 6.7.
- At follow-up, there were 77.3% fewer cases of hyperlipidemia (HYP), 85.7% fewer type 2 diabetics (DM), 46.2% fewer cases of hypertension (HTN) and 78.6% fewer cases of metabolic syndrome (MS) as compared to the time of surgery.
- For bariatric patients, AAS and MAS scores were 71 ± 13 and 77 ± 10.

Table 1. Clinico-demographic Information Pre & Post Bariatric Surgery

	Pre-Bariatric Surgery	Post-Bariatric Surgery	p-value
BMI	47.1 ± 6.1	30.9 ± 6.7	<0.0001
Waist	78.0 ± 39.3	68.7 ± 38.6	0.0567
Weight (kg)	131.2 ± 23.5	87.6 ± 21.3	<0.0001
ALT	33.6 ± 26.1	33.2 ± 26.3	0.7789
AST	26.2 ± 17.7	26.2 ± 12.5	0.8326
Total Cholesterol	192.4 ± 50.2	168.4 ± 44.0	0.0146
Diabetes Mellitus	14	2	0.0005
Hypertension	26	14	0.0005
Hyperlipidemia	22	5	<0.0001

Results

- Non-surgical control group (N=31) had BMI 29.4 ±5.4, AST 43.4 ± 21.1, ALT 59.5 ± 36.0, age 50.3 ± 10.3, 61.3% HYP, 9.7% DM, 32.3% HTN, and 16.1% MS.
- This group's AAS and MAS scores were 75.2 ± 15.4 and 79.7 ± 12.2.

Table 2. Activity Level Comparisons Between Post-Bariatric Surgery Patients & BMI Matched Controls

	Post-Bariatric Surgery	No Bariatric Surgery	Chi-Square
Age	52.4 ± 10.9	50.3 ± 10.5	0.8027
BMI	30.9 ± 6.7	29.5 ± 5.5	0.2809
Raw MAS Score	76.5 ± 9.9	79.2 ± 12.3	0.1866
Raw AAS Score	71.6 ± 13.1	74.6 ± 15.4	0.2589
AST	26.2 ± 12.5	43.9 ± 21.3	<.0001
ALT	33.2 ± 26.3	60.9 ± 35.8	<.0001
Total Cholesterol	168.4 ± 44.0	196.7 ± 37.3	.0090

- AAS and MAS scores between patients who had lost weight with bariatric surgery results and the controls were not different (p>0.05) (Table 2).
- However, AST, ALT and total cholesterol in the post bariatric surgery group were significantly lower than BMI-matched control (p<0.0001).

Conclusions

- After significant weight loss post bariatric surgery, activity level of these patients becomes similar to weight-matched controls.
- Scores for both post bariatric surgery and non-bariatric surgery groups showed that they were moderately active within the normal range of functioning.

INOVA FAIRFAX HOSPITAL

Psychiatric Disorders in Patients Undergoing Bariatric Surgery

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Background

- Obesity can be associated with psychiatric disorders such as depression.

Aim

- To determine the prevalence and association of psychiatric disorders in patients with excess body weight.

Methods

- Patients scheduled for bariatric surgery were invited to participate.
- For each patient, pre-surgical clinical and psychiatric data were collected.
- Follow-up data was available 1-year after surgery.
- Patients with psychiatric disorders were compared to those without psychiatric disorders.
- Mann-Whitney non-parametric test was used for comparison of numerical parameters.
- Prevalence of certain clinical and demographic events was validated using chi-square homogeneity test.

Results

- Four hundred ninety-nine patients were included: age: 42.8 ± 11.0, 20% male, 76% Caucasians, BMI 46.8 ± 10.8, ALT 32.5 ± 21.7 and AST 25.0 ± 14.3.

Results

- At baseline, a history of psychiatric disorder was documented in 214 (57%) patients (depression in 35% of patients, anxiety in 6% and other psychiatric diagnosis in 2.2%).
- Patients with a history of depression were older (p=0.0021), more likely to report history of drinking alcohol at baseline (p=0.0434) or 1-year after surgery (p= 0.0302), more likely to be female (p=0.0079) and Caucasian (p=0.0096) than patients without psychiatric history.

Psychiatric Diagnosis P-values (Compared to No Psychiatric Diagnosis Cohort)

	Depression	Anxiety	Alcohol/ Drug Abuse	Eating Disorder	Schizophrenia
Age	0.0021	0.4737	0.6159	0.9817	0.1515
Gender	0.0079	0.3003	0.9801	0.8179	0.5759
White	0.0096	0.3323	0.5346	0.5346	0.1081
Black	0.0307	0.2141	0.9393	0.9393	0.6391
Hispanic	0.9553	0.3466	0.7111	0.7111	0.8818
Asian	0.2719	0.6452	0.8657	0.8657	0.9665
Diabetes Mellitus	0.2351	0.0019	0.281	0.3657	0.5938
Hyperlipidemia	0.012	0.5408	0.5563	0.981	0.2207
Hypertension	0.0074	0.4952	0.9527	0.2062	0.3082
BMI	0.2142	0.5387	0.5915	0.5661	0.1119
Waist	0.2816	0.9145	0.7525	0.4462	0.5416
ALT	0.4116	0.9373	0.974	0.1942	0.3361
AST	0.6462	0.7259	0.0664	0.0254	0.3443
AST/ALT	0.1218	0.9563	0.0561	0.1923	0.5272
Glucose	0.3063	0.7459	0.2717	0.5887	NA*
Cholesterol	0.1989	0.3378	0.0706	0.4271	0.1275
Triglycerides	0.0452	0.6646	0.3633	0.2087	0.2112
Alcohol Intake Before Weight Reduction Surgery	0.0434	0.8548	0.7996	0.8702	0.2611
Alcohol Intake 1 Year Post Weight Reduction Surgery	0.0302	0.5641	0.8772	0.8058	0.8772
Smoking	0.5853	0.0933	0.2846	0.4834	0.7639
Fatty Liver	0.6943	0.2765	0.1206	0.0532	0.8166
Fibrosis	0.363	0.6918	0.0931	0.3633	0.6555
NASH	0.0633	0.8812	0.9516	0.3255	0.5745

Results

- Additionally, 45% of the cohort (N=223) reported history of alcohol consumption.
- The majority of these patients (98.7%) reported 0-2 drinks of alcohol per day, and only 3 patients reported >2 drinks per day.
- Patients who reported a history of alcohol consumption were more likely to also report a history psychiatric disorders (48.5% vs. 39.6%, p= 0.0093).
- Furthermore, those who reported a history of alcohol consumption at baseline were more likely to drink 1-year after surgery (10.81% vs. 2.74%, p= 0.0128).
- In multivariate analysis, predictors of alcohol consumption were a history of psychiatric disorders, younger age and lower AST/ALT ratio (model p-value= 0.02039).
- On the other hand, variables independently associated with a history of psychiatric disorders included: alcohol consumption, female gender, having type 2 diabetes or hyperlipidemia as well as a higher AST/ALT ratio (model p-value=0.0010).

Conclusions

- Patients undergoing bariatric surgery seem to have high prevalence of depression and anxiety.
- Although excessive alcohol use (>2 drinks/day) is rare, alcohol consumption seems to be associated with psychiatric disorders and continues after surgery.

CANCER RESEARCH PROGRAM

INOVA FAIRFAX HOSPITAL

Stabilization Chemistry for Universal Application to Protein, RNA, DNA and Morphology Preservation

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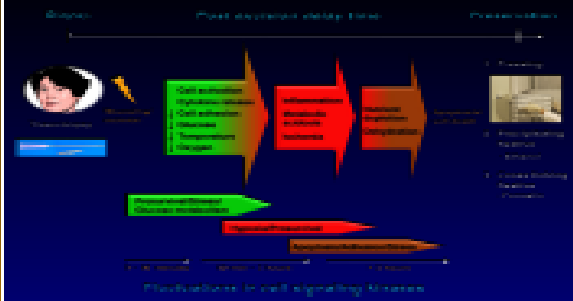
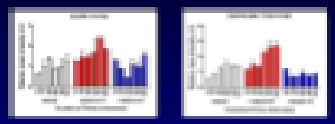
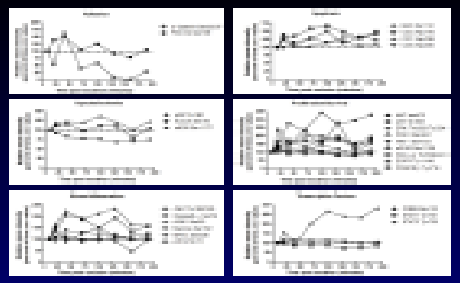
Excised Tissue is Alive!



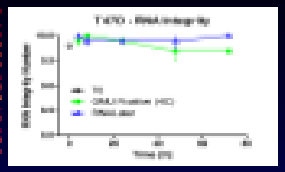
It is a well known but under-appreciated fact that tissue stays alive and reactive during the immediate ex vivo period. Thus, changes in protein or nucleic acid amount and modification will occur that are purely based on the tissue's response to stress, lack of oxygen, acidosis etc. We have previously shown that protein posphorylation in excised tissue can change in a matter of minutes [1,2].



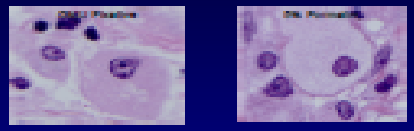


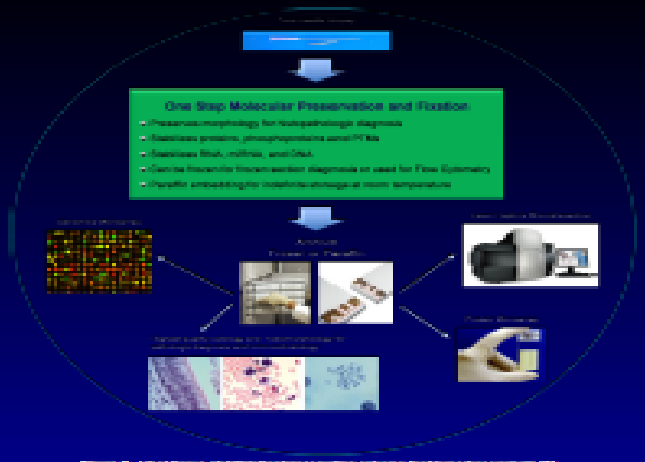
Development of a Multi-purpose Stabilizing Agent

Stabilization of RNA Integrity



Preservation of Morphology





Stabilization of Protein Phosphorylation

Compatibility with Histochemistry

Conclusions

There is an urgent need to develop a one step preservation chemistry that will maintain cellular and tissue morphology, as well as prevent fluctuations or degradation in tissue biomarkers, post excision. To date the best method of tissue preservation is snap freezing in liquid nitrogen. However, in a standard clinical setting this is often not feasible. To address this need we are developing a fixation chemistry that preserves proteins, RNA and DNA and their respective modifications, as well as permitting cryosectioning while maintaining cellular morphology for pathological diagnosis.

While further development is necessary our current multipurpose chemistry is superior in stabilizing phosphoproteins while preserving good morphology. While further enhancing preservation properties in these areas we are currently also focussing on effective fixation of nucleic acids. Thus, we hope that in the near future, our fixative can be a starting point for processing all pathologic specimens into a standard paraffin block while preserving, and archiving, all classes of macromolecules for molecular profiling.

References & Acknowledgements

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Discovery of DCIS progenitor cells: the target for a new therapeutic trial

PINC Trial: Preventing Invasive breast Neoplasia with Chloroquine

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GEORGE MASON UNIVERSITY

INOVA BREAST CARE INSTITUTE

Abstract

A majority of, if not all, invasive breast cancer progresses from a DCIS precursor stage. We have a clinical trial underway for the clinical evaluation of a unique therapeutic strategy for Human Breast Ductal Carcinoma In Situ (DCIS). Our novel technologic approach allows us to monitor therapy at the level of molecular signaling and biologic invasive function of the living DCIS cells ex vivo, pre and post treatment.

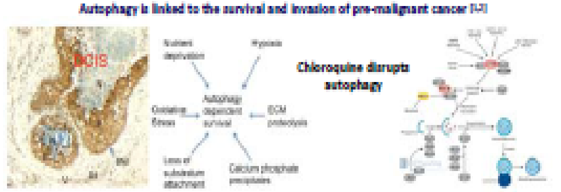
Our DCIS therapeutic target is the autophagy pathway, and the treatment agent is oral Aralen (chloroquine phosphate). The choice of this pathway inhibitor is based on our new data using living human DCIS neoplastic cells grown in organoid culture. These data support the hypothesis that the autophagy pathway may be a key regulator for emergence of invasion and epithelial cell survival in the hypoxic DCIS ductal niche. These findings reveal, for the first time, that individual patient's fresh human DCIS neoplastic cells, if removed from the duct niche, already possess the full capacity for functional ex vivo tissue invasion. We have propagated and characterized the invasive DCIS epithelial neoplastic cells possessing progenitor cell characteristics. Protein array analysis of 48 cell signaling kinase endpoints, representing stem cell markers, autophagy, adhesion, invasion, and prosurvival pathways, revealed a set of activated signaling pathways, consistent with a progenitor character. Full genome molecular cytogenetics studies (Illumina SNP microarrays) with a plurality of human DCIS tissue donors verified that invasive DCIS cells with progenitor cell features (3-D pseudoductal and spheroid formation) show cytogenetic abnormalities compared to the patient's matched normal breast tissue.

Our trial examines the safety and effectiveness of Aralen, alone or in combination with tamoxifen, administered for a 3 month period to patients with low, intermediate, or high grade DCIS. Patients with high grade ER+ DCIS receive tamoxifen plus Aralen. ER- patients receive Aralen alone. Patients with low grade ER+ DCIS receive tamoxifen. At the conclusion of the treatment period, all patients receive standard of care surgical therapy. MRI is performed before and after the treatment period. 'Effectiveness' in this accelerated trial is measured at the molecular level. Using our unique protein microarray technology, the activated state of 100 proteins associated with autophagy, hypoxia, apoptosis, angiogenesis, invasion, and cell cycle pathways are measured before and after therapy within the microdissected epithelial and stromal compartments. In parallel, DCIS living organoids are harvested and scored for a) invasive potential in human breast stroma ex vivo, b) progenitor cell yield and growth, and c) growth in NOD SCID murine xenotransplantation. Full genome molecular cytogenetics is conducted before and after therapy.

Conclusion

The unique accelerated study design provides immediate molecular and biologic feedback about the candidate strategies aimed at eradicating intraductal neoplastic cells within breast premalignant lesions. This trial, if successful, can support a future strategy under which a woman would be treated for a 3 month period with an oral agent (Aralen), that would suppress, or biochemically eradicate, any occult or overt premalignant lesions. A relatively non-toxic systemic therapy that effectively treats DCIS could significantly reduce the risk of subsequent development of breast cancer in the same patient.

Autophagy is linked to the survival and invasion of pre-malignant cancer [1-2]



1. Hypoxia and nutrient stress. Proliferating ductal epithelial cells accumulating within the breast duct do not have access to the vasculature outside the duct. High grade DCIS is associated with central necrosis, and the accumulation of lipofuscin. Autophagy is a pathway activated to promote survival in the face of hypoxia and nutrient stress.

2. Anoikis. Anoikis is the triggering of apoptotic cell death for cells that have been separated from their normal adhesion substratum. Normal glandular epithelial cells require attachment to, or association with, the basement membrane ECM for continued survival. During ductal hyperplasia and dysplasia epithelial cells exist within the duct at a substantial distance away from association to the peripheral basement membrane. Autophagy has been shown to be a key survival regulator for cells deprived of an anchoring substratum and may play an important role for cell survival in any anchorage independent state.

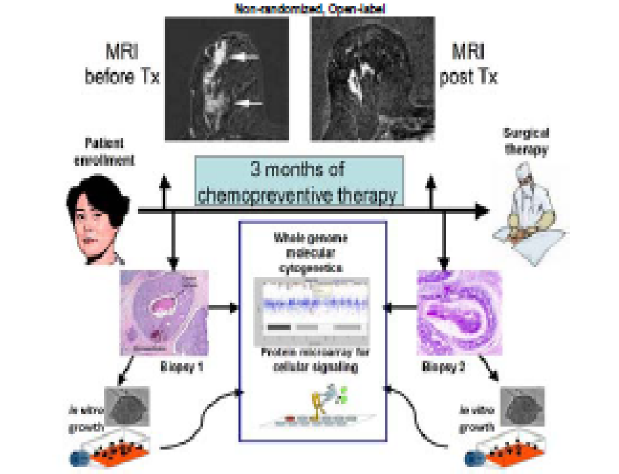
3. Matrix degradation. High grade DCIS, microinvasion, and overt carcinoma invasion is associated with interruptions, remodeling, and enzymatic breakdown of the basement membrane and the stromal ECM. Autophagy may facilitate cell movement through areas of degraded matrix by the phagocytic processing of matrix breakdown fragments.

4. Calcium. Microcalcifications are mammographic indicators of high grade DCIS and calcium phosphate precipitates are potent inducers of autophagy. Based on these established mechanistic roles, autophagy constitutes a novel target for treating DCIS and arresting DCIS transition to overt invasion.

Clinical Trial Design

ClinicalTrials.gov Identifier: NCT01023477

Non-randomized, Open-label



The purpose of this phase I/II study is to test the hypothesis that inhibiting the autophagy pathway in DCIS will reduce the capacity of DCIS to survive and invade. The study will examine the safety and effectiveness of neoadjuvant chloroquine and/or tamoxifen administration for a three month period to patients with low, intermediate grade, or high grade DCIS. We will evaluate whether these treatments will reduce the DCIS lesion size as judged by MRI or histology, and suppress survival of DCIS progenitor cells ex vivo.

Treatment Arms

Tamoxifen (20mg/day for 12 weeks): ER+ low grade DCIS

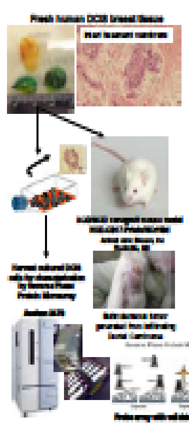
Chloroquine (500mg/week for 12 weeks): ER- any grade DCIS

Tamoxifen+Chloroquine: ER+ high grade DCIS

Inclusion criteria:
- Female
- DCIS, any grade
- No previous CQ in past 24 months
- No hx of invasive cancer in last 5 yrs.
- Normal LFT
- No underlying ocular/retinal pathology

Exclusion criteria:
- Prior hx of chemotherapy, hormonal therapy, or radiation
- Hx of previous breast surgery in immediately adjacent area
- Hx of allergic reaction to tamoxifen or chloroquine

Methods for Pre-Clinical Data



Human DCIS lesions contain pre-existing carcinoma precursor cells

Our model system for ex vivo organoid culture of living human ductal carcinoma in situ (DCIS) lesions, without enzymatic treatment or sorting, induced the emergence of neoplastic epithelial cells exhibiting the following characteristics:

a) Spontaneous generation of hundreds of spheroids and duct-like 3-D structures in culture within 2-4 weeks.
b) Tumorigenicity in NOD SCID mice.
c) Cytogenetically abnormal (copy number loss or gain in chromosomes including 1, 5, 6, 8, 13, 17) compared to the normal karyotype of the non-neoplastic cells in the source patient's breast tissue.
d) *In vitro* migration and invasion of autologous breast stroma.
e) Up-regulation of signal pathways linked to, and components of, cellular autophagy.

Figure 1. Model system for generating and characterizing DCIS progenitor cells.

Pre-clinical Data

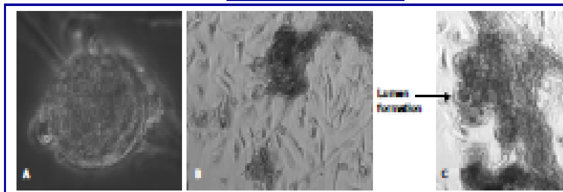


Figure 2. Human breast DCIS *in vitro* culture. Differential structures formed *in vitro* reflect spheroids (A), ductal-like clusters (B), 3-Dimensional structures (C).

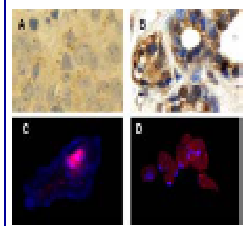
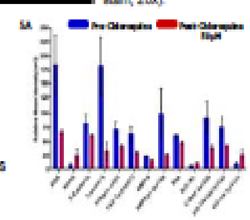
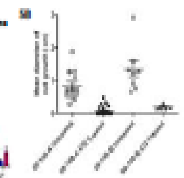


Figure 3. Autophagy markers are increased in DCIS. (A) IHC of a primary DCIS lesion showing punctate staining within the cytoplasm for LC3B, a protein associated with autophagosome formation (anti-LC3B, 100x). (B) Beclin1 positive human DCIS derived mouse xenograft tissue (100x). (C) Fluorescence microscopy shows accumulation of LysoTracker Red dye within the organelles of the inner cell mass of a 3-D structure (20x). (D) Diffuse accumulation of LysoTracker Red in autophagic compartments and lysosomes (red=LysoTracker Red; blue=DAPI nuclear counter stain, 20x).

Figure 4. Pedunculated spheroid with central necrosis in cultured DCIS organoid.





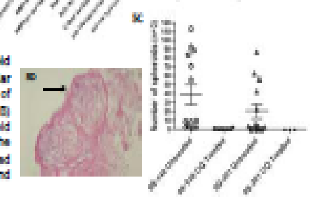


Figure 5. Chloroquine treatment of DCIS organoid cell cultures is associated with cellular degeneration and necrosis. (A) RPMA analysis of cell signaling proteins pre/post CQ (mean±SEM). (B) Patch diameter of outgrowths ±CQ. (C) Spheroid formation ±CQ. (D) DCIS organoid cultured in the presence of chloroquine for 6 months showed complete absence of cellular outgrowths and degenerated cells within the duct (arrow) (10x).

Conclusions

- We have developed a model system for reliably revealing cytogenetically abnormal, invasive progenitor cells from fresh human DCIS which we are able to propagate in culture.
- Using this model system we have identified the autophagy pathway as a therapeutic target for DCIS. Chloroquine, an inhibitor of autophagy, suppresses the growth and survival of DCIS progenitor cells.
- *In vitro* models of chloroquine treatment confirm our hypothesis that autophagy is necessary for survival of intra-ductal DCIS cells and provides justification for this PINC trial.
- A relatively non-toxic, systemic, short term therapy that effectively treats DCIS, as proposed herein, would be hypothesized to significantly reduce the risk of subsequent development of breast cancer in the same patient.

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CARDIAC SURGERY RESEARCH PROGRAM

INOVA HEART AND VASCULAR INSTITUTE

Discovery of Mitochondrial Protein Biomarkers of Atrial Fibrillation Using Unique Human Tissue Samples

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[1]George Mason University, Manassas, VA; [2]Inova Heart & Vascular Institute, Falls Church, VA

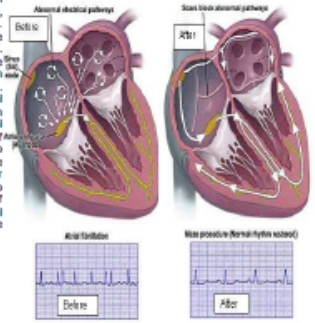
Overview

The objective of this project is to utilize a unique study set of human clinical specimens from patients with and without atrial fibrillation (AF) for the identification of differentially expressed mitochondrial associated proteins that once validated may serve as biomarkers of AF. Our research strategy is based on a comparative mass spectrometric (MS) analysis and reverse-phase protein microarray (RPMA) assay of mitochondrial protein fractions isolated from samples of right atrial tissue obtained from AF patients and non-AF control subjects. Potentially differentially abundant proteins determined by global MS spectral counting-based comparative analysis were verified using targeted RPMA assays. The use of high resolution MS in combination with novel protein microarray technology for differentially expressed protein identification and verification, respectively, constitutes a new and effective strategy for discovery of biomarkers of a variety of human diseases such as AF.

Introduction

AF is the most common of sustained arrhythmias encountered in clinical practice with an occurrence of >25% after open heart surgery and results in significant increase of risk for stroke, premature death and heart failure. Despite a high success rate, the Maze procedure (Figure 1) does not cure AF. More than 2.2 million individuals in the United States are affected with AF with an expected ~6 million patients by 2050. Multiple studies suggest that atrial mitochondria have a significant role in the pathophysiological processes of atrial fibrillation, including our finding of mitochondria dysfunction in response to simulated ischemia (1). Despite extensive research, it is unclear whether mitochondrial changes are secondary to the general structural remodeling of atrial tissue, or if mitochondrial dysfunction is related to the occurrence of atrial fibrillation.

Figure 1: Illustration of the electrical circuitry in an AF patient before and after Maze surgery



Methods

Samples and Mitochondria Enrichment: Right atrial tissue samples were acquired from 10 patients undergoing the Maze surgery and from 10 patients undergoing another type of cardiac surgery. The tissue samples were flash frozen in liquid nitrogen in the operating room. 200mg of each tissue sample were lysed using a barocycler (Figure 2) (Barocycler, Pressure Biosciences, South Easton, MA). The mitochondria proteins were enriched from the cell lysates using a commercial kit (Mitochondria Isolation Kit, Biochain Inc, Hayward, CA). RPMA was used to determine the enrichment efficiency by targeted assays of cytosolic and mitochondrial protein markers.

LC-MS/MS Analysis: Mitochondria proteins were reduced and alkylated followed by trypsin digestion. A 10mg aliquot of each digest was analyzed by LC-MS/MS with a 2-hour HPLC gradient and a top 8 data dependent acquisition method using a Thermo LTQ-Orbitrap mass spectrometer. Internal protein and peptide standards were used for quality control. The MS data were searched against a human protein database (NCBI) with SEQUEST and comparatively analyzed based on MS/MS spectral counts using Scaffold (Proteome Software, Inc.).

RPMA Analysis: Mitochondrial lysates were printed on nitrocellulose coated slides (Whatman, Inc, Sanfort, ME) using an 2470 Arrayer (Aushon BioSystems Ins., Billerica, MA) outfitted with 350 µm pins. Blocked slides were then incubated with 4 different antibodies against candidate protein biomarkers identified by MS as being differentially expressed. An automated stainer (Dako Cytomation, Carpinteria, CA, USA) was used. Fluorescent IRDye® 680 Streptavidin (LI-COR Inc., Lincoln, Nebraska, USA) was used as the detection system. Stained slides were scanned with NovaRay Image Acquisition Software (Alpha Innotech, San Leandro, CA, USA). Acquired images of each slide were analyzed using MicroVigene software (Vigenetech, Carlisle, MA, USA).

Results

Candidate Biomarker Discovery: Approximately 600-700 proteins were identified in each mitochondria digest by MS analysis. Approximately 5% of the identified proteins were found to be potentially differentially-expressed (t-test p-value<0.01) in the analysis of peptide/protein relative abundances based on spectral counts (with manual confirmation): **28** proteins were identified to be more abundant in the AF right atrial tissue samples compared with non-AF right atrial tissue samples, while **4** proteins were identified to be more abundant in the non-AF right atrial tissue samples. A subset of these proteins and associated spectral counts are shown in Table 1.

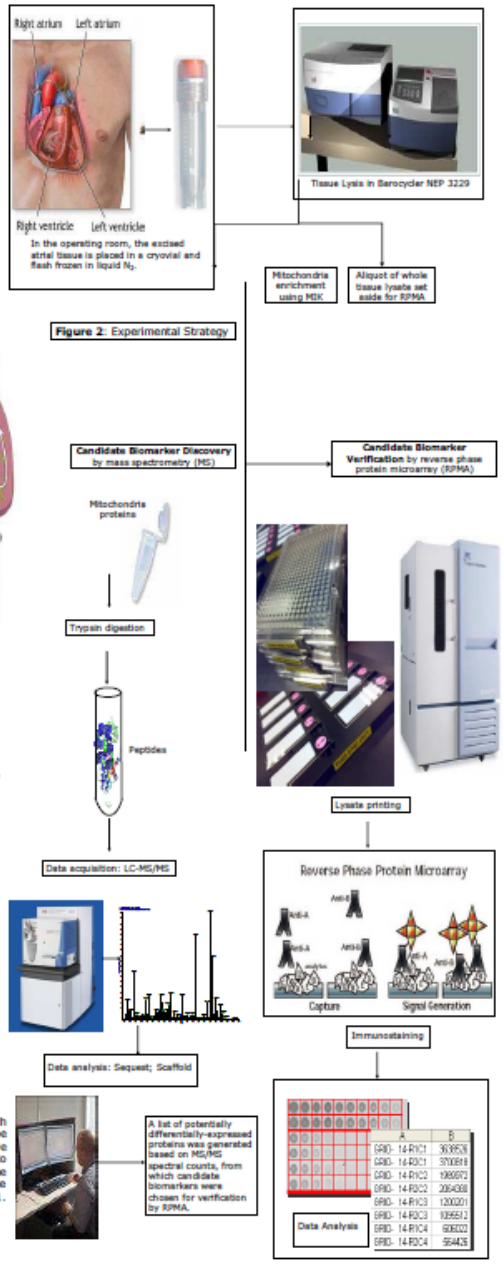


Figure 2: Experimental Strategy

Table 1: Candidate Biomarker Discovery Results (Global MS Proteomics - Spectral Count Analysis)

	Number of Assigned MS/MS Spectra	
Protein	non-AF Right	AF Right
crystallin alpha beta	32	102
desmin	28	109
acyl-coenzyme A dehydrogenase	28	112
glyceraldehyde 3-phosphate dehydrogenase	120	89
gelsolin isoform b	69	51
chaperonin containing TCP1 subunit5 (CCT5)	5	46
destrin	2	19
four and a half LIM domain 2 (FHL2)	0	11
heat shock protein 27 (HSP27)	0	17

Candidate Biomarker Verification: We chose four potentially differentially abundant proteins (highlighted in Table 1), based on their importance in energy production and regulatory association with atrial ion channels, for verification of differential abundance (AF>non-AF) using targeted RPMA assays of an independent tissue sample set (Figure 3). Antibodies used for RPMA analysis were validated by Western blots.

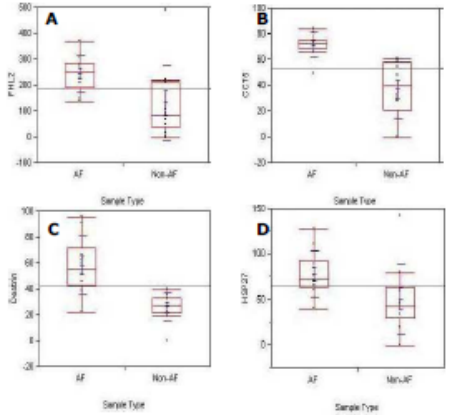


Figure 3: Box plots of RPMA measurements of the four selected candidate biomarker proteins (Panel A: FHL2, Panel B: CCT5, Panel C: Destrin, and Panel D: HSP27). These proteins were measured to be more abundant in the enriched mitochondrial preparations of right atrial tissue from AF patients AF (left) compared with those from non-AF patients (right). The measured differential abundances are statistically significant ($p \leq 0.05$), and these results confirm those obtained by MS analyses.

Discussion

Involvement in AF development has been reported for LIM domain-containing proteins such as FHL2, which has a role in atrial arrhythmogenesis (2), and for HSP27, which once induced is reported to protect against atrial remodeling (3). The latter observation is consistent with the greater abundance in AF atrial tissue determined in our work. *In contrast but potentially equally significant, ours is the first report of* ***destrin*** *and* ***CCT5*** *associated with AF.* These findings will be followed up with further experimental and bioinformatic analyses.

This first comparative analysis of mitochondria proteins from unique human atrial tissue samples from AF patients and controls has yielded four candidate biomarkers and new insights into the changes that occur in atrial mitochondrial protein expression as a result of AF onset. We plan to use MS and RPMA to verify the differential expression of these four (and other) candidate biomarkers in a larger blinded sample set and ultimately in patient serum samples. There is significant potential impact of this study for atrial fibrillation with respect to new biomarkers of the risk to develop arrhythmia as well as biomarkers for new drugs, device therapies and hybrid treatment strategies.

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Presented at Meeting of The Association for Mass Spectrometry: Applications to the Clinical Laboratory, Inc. 2010

INOVA HEART AND VASCULAR INSTITUTE
Inova Fairfax Hospital

Presented at the annual meeting of the Society of Thoracic Surgeons 2010

Late Stroke/TIA and Major Bleeding Events after Surgical Ablation of AF: Is There a Role for the CHADS Score?

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INTRODUCTION

The Heart Rhythm Society (HRS) guidelines recommend continuing warfarin following catheter ablation whenever patients' CHADS Score ($CHADS_2$) is ≥2, however there are no clear recommendations regarding patients after surgical ablation. Therefore, managing anticoagulation following surgical ablation that includes the removal/exclusion of the LA appendage is challenging.

PURPOSE

The purpose of this study was to quantify the applicability of the $CHADS_2$ in determining anticoagulation strategies following surgical ablation procedures.

METHODS

- N=416 with surgical ablation procedures (364 pts: Cox-Maze III-IV procedure, 52 pts: Left atrial ablation only)
- A prospective, longitudinally designed study where $CHADS_2$ were calculated preoperatively for all patients and $CHADS_2$ were recalculated if required during follow up
- 16.3% of patients presented with history of Stroke/TIA
- Follow up clinical information on rhythm, anticoagulation medication, major bleeding and embolic stroke/TIA was obtained every 3 months after the blanking period (blanking period defined as per HRS guidelines, i.e. the first 3 months after the surgical ablation)
- Rhythm and medication status for patients with thromboembolic or bleeding events was calculated at the time of the first event
- Independent samples t-tests were used to compare event groups on $CHADS_2$ and logistic regression was conducted to determine predictors of events

RESULTS

- Mean follow up of 31.32 (±17.3) months
- Embolic stroke/TIA events occurred in 4 patients (6.45 events per 1000 patient years) (Fig 1)
- 23 major bleeding events occurred in 17 patients (21.18 events per 1000 patient years) with 65% of the major bleeders on warfarin at the time of event (Fig 2)
- There was *no significant difference* in the mean $CHADS_2$ between the Stroke/TIA event and non-event group (0.75 vs 1.47 respectively, p=0.21) (Fig 3)
- There was a *significant difference* in the $CHADS_2$ between the event bleed group and the non-event group (2.25 vs 1.43 respectively, p<0.01) (Fig 3)
- Logistic regression models were used to determine whether age, hypertension (HTN), diabetes, Stroke/TIA, CHF, $CHADS_2$, rhythm and warfarin status were *significant predictors* of either event
- No simple or 2-way effects of these variables were predictive of Stroke/TIA
- The interaction term CHF/HTN (p<0.009), was the *most significant predictor* of a major bleed (Wald=6.91)

Figure 1: Describing First Thromboembolic Event and Rhythm Status at Time of Event

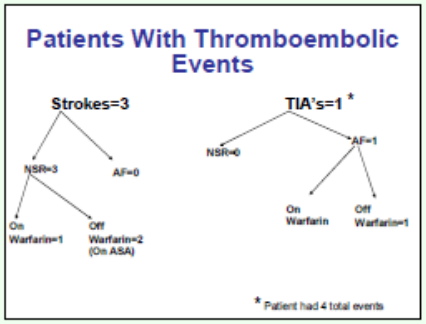


Figure 2: Bleeding, Rhythm and Warfarin Status

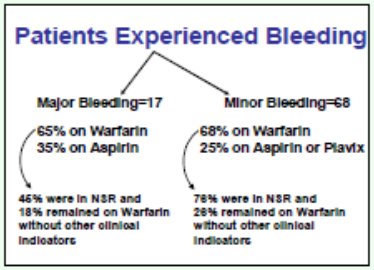
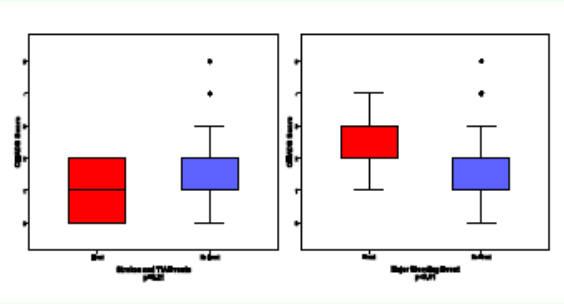


Figure 3: $CHADS_2$ and Events



CONCLUSIONS

- A new risk algorithm for thromboembolic events should be developed for patients following surgical ablation.
- The number of thromboembolic events following surgical ablation is very low, unrelated to the $CHADS_2$ or rhythm status.
- This together with the higher rate of major bleeding events in the $CHADS_2$ ≥ 2 group raises questions regarding the applicability of the HRS guidelines for patients following surgical ablation and in particular after the Cox Maze III/IV procedure.
- A large scale randomized study is required to determine the risk/benefit of anticoagulation, CHADS score, thromboembolic events and bleeding for patient following surgical ablation especially when the LAA was excluded and high success rate is expected.

There are no conflicts of interest. No funding was received for this study

The Implementation of a Comprehensive Clinical Protocol Improves Long Term Success Following Surgical Treatment of Atrial Fibrillation

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INOVA HEART AND VASCULAR INSTITUTE
Inova Fairfax Hospital

Cardiac Surgery Research

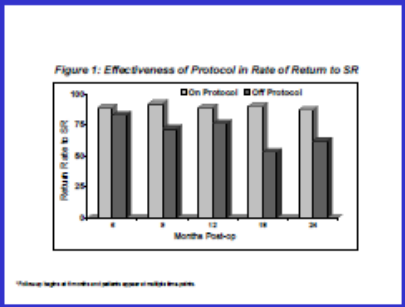
ABSTRACT

OBJECTIVE: The maze procedure performed for the treatment of atrial fibrillation (AF) as either stand alone or combined with other surgery is becoming commonplace. Post discharge, patients are often being followed by their cardiologists who are unfamiliar with the nuances of the surgical procedure as well as the management of patients medical regimen and recurrence of post surgery arrhythmia. We sought to determine the effectiveness of a post discharge protocol designed to coordinate patient management between the cardiac surgeon and cardiologist.

METHODS: Our atrial fibrillation surgery center captures all patients having the maze procedure into a registry designed to provide longitudinal comprehensive clinical follow ups at 3, 6,9,12,18, 24 months. The prospective follow up information collected includes: rhythm status, medications and interventions. Letters with the post discharge protocol as well as letters recommending further interventions required to comply with the protocol were sent to the cardiologists, at the follow up time points

RESULTS: Currently, we have 334 patients (multiple surgeons) in our registry with over 1600 records and follow up rhythm status information. Independent of the clinical protocol, the return to SR was 86%, 84%, 84% and 84% at 6, 12, 24 and last follow up respectively (mean time to FU=25.1 months). Significantly improved results were documented for patients who were treated according to the protocol with SR rate of 90% vs 81%, 88% vs 76%, 90% vs 65% and 89% vs 79% at 6, 12, 24 and last follow up respectively (Figure 1). Failures to complete the protocol was documented in 59 % of the patients in AF, with the most common deviations being anti-arrhythmic drug treatment, any attempt of cardioversion and placement of patients on rate control regimen prematurely.

CONCLUSION: The success rate of the maze procedure is significantly better in patients that were treated according to the clinical protocol. Clinical coordination with the cardiologist is challenging but important; therefore, centers performing the surgical treatment for AF should make the effort to implement a comprehensive clinical algorithm to improve the outcome following the maze procedure



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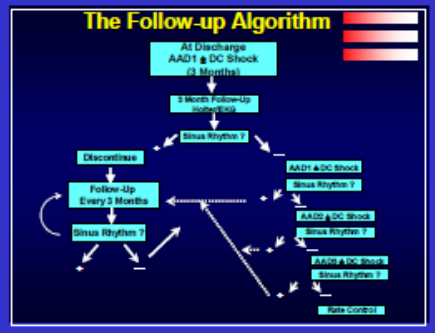
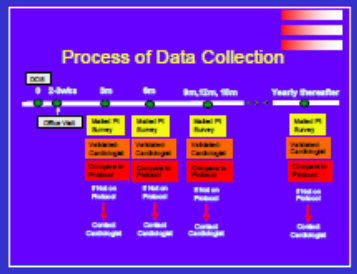
HISTORY

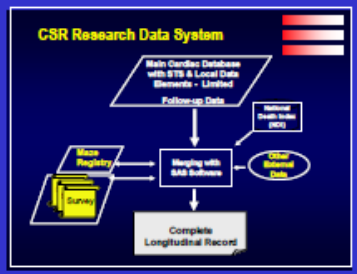
- Jan 2005 to Aug 2006, N=142 surgical maze procedures
- NSR documented in 108 (91%) patients.
- Only 3 of the 11 patients who remained in atrial fibrillation/flutter (27%) were followed by any arrhythmia protocol
- 44 patients (40%) in sinus rhythm were found to be pharmacologically managed with AA's without a clear indication.



FOLLOW-UP

- Office visit 10 days post discharge with rhythm and medication documentation
- Mailed surveys to patients to obtain Health Related Quality of Life (HRQL), rhythm status , clinical events and medications at 3, 6, 9, 12, 18, 24 months and yearly thereafter,
- Intermittent office or hospital visits collected via physician office, patient or hospital. Clinical information recorded.





CHANGE IN SCOPE OF FOLLOW-UP

From patient reported single question about rhythm

↓

To patient reported rhythm, medications, and events

↓

To patient reported rhythm, medications, events as well as documented physician notes/tests

↓

To patient reported rhythm, medications, events, documented physician notes/tests as well as determination if on protocol

RESULTS

- ✓Since 2005, 366 patients have had surgical ablation
- ✓243 have a concomitant surgery with maze, 78 have had a stand alone maze procedure and 45 had concomitant surgery with PVI
- ✓~ 2000 clinical records have been generated
- ✓ Regardless of protocol, return to SR was 89%, 87%, 88%, 82% and 85% at 6,9,12,18 and 24 months respectively
- ✓ Improved results were noted for patients treated with the protocol:

92% vs 85%, 91% vs 78%, 91% vs 78%, 91% vs 58% and 90% vs 65% at 6,9,12,18 and 24 months respectively (p<.05).

CONCLUSION

- The success rate of the maze procedure is significantly better in patients that were treated according to the clinical protocol
- A protocol provides a means to evaluate the cost effectiveness of a procedure
- Failure to follow a protocol does not allow practitioners to have a clear understanding of the outcomes from the maze procedure

ADVANCED LUNG DISEASE PROGRAM

INOVA HEART AND VASCULAR INSTITUTE

Prevalence of Unsuspected Coronary Artery Disease in Patients with Idiopathic Pulmonary Fibrosis

Inova Advanced Lung Disease & Transplant Program

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Abstract

There is no effective treatment for idiopathic pulmonary fibrosis (IPF). IPF can be associated with a variety of comorbidities, including coronary artery disease (CAD). Diagnosing and treating CAD at an early stage may improve mortality in IPF patients. We sought to determine the prevalence of known and previously unsuspected CAD in a cohort of IPF patients being evaluated for lung transplantation.

Methods: We performed a retrospective review of IPF and COPD (control) patients undergoing left heart catheterization (LHC) as part of their lung transplant evaluation. Patients were stratified into those with known and unknown CAD before evaluation. Major cardiac risk factors were assessed. Patients were categorized as having significant (≥50% stenosis), mild (<50% stenosis), or no CAD based on LHC results.

Results: 73 IPF patients and 66 COPD patients qualified for the analysis. 16% (12/73) of IPF patients and 18%(12/66) of COPD patients were known to have CAD before transplant evaluation. In patients with unknown CAD status, 59% (36/61) of IPF patients were found to have some form of CAD at LHC, compared to 31%(17/54) of COPD cases (p<0.003). 18%(11/61) of IPF patients were found to have significant CAD vs. 9% (5/54) of COPD patients (p<0.004). There were no significant differences in prevalence of cardiac risk factors between IPF and COPD, except for smoking history (COPD 97% vs. IPF 51%, p=0.001). Excluding transplant recipients, IPF patients with significant CAD had increased mortality (median survival 1.26 years from LHC) vs. mild or no CAD (p=0.02).

Conclusion: IPF has a significant association with CAD even after adjusting for CAD risk factors. There is a high prevalence of unsuspected CAD in IPF patients. Patients with both IPF and significant CAD have an increase in mortality.

Introduction

- IPF is a progressive, fibrotic disorder in which there is no effective treatment.
- IPF can be associated with a variety of comorbidites, including CAD.
- CAD may contribute to mortality in IPF patients.
- Diagnosing and treating CAD at an early stage may improve mortality in IPF patients.
- The goals of our study were to;
  - determine the prevalence of known and previously unsuspected CAD in IPF patients undergoing lung transplant evaluation.
  - Establish whether IPF is an independent risk factor for CAD by controlling for common CAD risk factors.
  - Assess the impact of CAD on the outcomes of patients with IPF.

Methods

- Retrospective review of IPF patients who underwent LHC as part of pretransplant evaluation for the period September 2003 to July 2008.
- COPD patients, who were similarly evaluated during the same period, were used as a control cohort.
- Major cardiac risk factors, including smoking, hypertension, diabetes mellitus, hypercholesterolemia and family history of CAD were assessed.
- Patients were noted to have had a diagnosis of CAD prior to pretransplant evaluation.
- Based on LHC results, patients were categorized as having
  - significant CAD (≥50% stenosis in one or more major coronary arteries),
  - mild CAD (<50% stenosis)
  - no CAD.
- Cumulative probability of death after cardiac catheterization was calculated using Kaplan-Meier curves for patients with significant CAD vs. mild or no CAD.
- Statistical analyses were conducted using GraphPad Prism and SAS.

Results

- 73 IPF patients and 66 COPD patients qualified for the analysis.
- 16% of IPF patients and 18% of COPD patients were known to have CAD prior to transplant evaluation.
- In patients with unknown CAD status, 59% of IPF patients were found to have CAD at LHC, compared to 31% of COPD patients (p=0.003). Demographics of IPF patients with unknown coronary artery disease status prior to left heart catheterization are shown in table 1 (N=61)
- 18% of IPF patients were found to have significant CAD compared to 9% of COPD patients (p<0.004).
- There were no significant differences in prevalence of cardiac risk factors between IPF and COPD patients except for smoking history (97% COPD vs. 51% IPF(p=0.001).
- Excluding transplant recipients, IPF patients with significant CAD had increased mortality (median survival 1.26 years from LHC) vs. mild or no CAD (p=0.02) (figure 1).

	CAD Classification			
	None (n=25)	Non-significant* (n=25)	Significant** N=(11)	P
Age (mean ± SD)	59.0 ± 8.5	59.2 ± 5.8	65.0 ± 5.2	0.018
Male (%)	15 (60.0)	19 (76.0)	10 (90.9)	0.139
Race	15 (60.0)	24 (96.0)	7 (63.6)	0.008
Body Mass Index, kg/m²	28.5 ± 5.1	29.5 ± 3.6	27.9 ± 4.5	0.554
FVC%	55.9 ± 13.2	63.9 ± 14.5	57.8 ± 19.9	0.167
FEV1%	59.7 ± 14.1	67.4 ± 14.6	59.9 ± 14.4	0.120
DLco%	29.8 ± 10.1	35.4 ± 17.4	35.1 ± 15.2	0.348

Table 1. Demographics of IPF patients with prior unknown CAD status

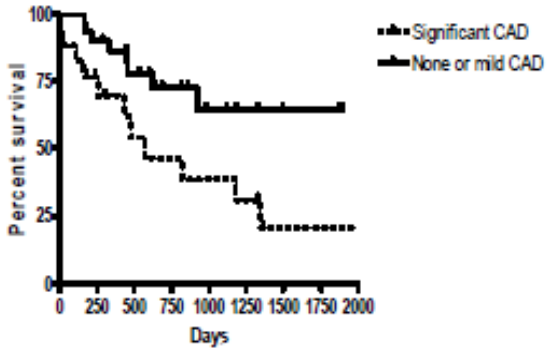

Fig 1. Kaplan Meier curves: Survival of IPF patients with and without CAD (p=0.02)

Conclusion

- We confirm the association of IPF with CAD by comparing IPF patients to a control cohort of COPD patients.
- A significant portion of the IPF subjects had unsuspected CAD at LHC.
- The increase prevalence of CAD in IPF was not explained by common cardiac risk factors.
- IPF therefore appears to be an independent risk factor for CAD.
- The presence of significant CAD in IPF patients is associated with an increase in mortality (even when treated).
- It is possible that significant undiagnosed and untreated CAD has an even greater impact in IPF outcomes.
- Awareness of this association and aggressive screening for CAD in IPF may help to improve outcomes in IPF patients.

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Inova Advanced Lung Disease & Transplant Program

Native Lung Complications in Single Lung Transplant Recipients and The Role of Native Lung Pneumonectomy

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Background

- 17,000 lung transplantations were performed between January 1995 and June 2006, over half of which were single lung transplants (SLT)
- 5 year survival with BLT is thought to be superior to SLT (54% vs. 46%)
- Native lung complications (NLC) may account for some of this apparent difference in survival
- Despite the large number of SLTs and the propensity for NLC, the impact and management of these remains poorly defined.
- Native lung pneumonectomy (NLP) is one therapeutic option in select cases.

Purpose

- To examine the incidence and nature of NLC in a large cohort of SLT recipients
- To determine the effect of NLC on survival of SLT recipients
- Report on the role and results following NLP for NLC

Methods

- Retrospective cohort of all patients undergoing SLT at Inova Fairfax hospital from January 1, 1998 through June 30, 2006
- All patients developing significant NLC were identified
- Significant NLC were defined as those resulting in hospitalization or death
- Post-transplant and post-complication survival were the primary endpoints
- A separate analysis was performed on those patients with NLC treated with NLP
- The decision to perform NLP was individualized based on each patients unique clinical circumstance.

Results

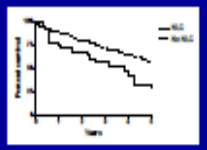
- 180 patients underwent SLT
- 25 (14%) developed NLCs
- 11 required NLP

- Indications for NLCs
  - Pneumothorax (8/25)
  - Malignancy (7/25)
  - Aspergilloma (4/25)
  - Pneumonia (3/25)
  - BPF (3/25)
  - Pulmonary embolism (1/25)

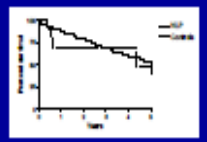
Patient Demographics

	Native Lung Pneumonectomy	All Native Lung Complications	Control	
	N (%) or mean (range)	N (%) or mean (range)	N (%) or mean (range)	P
No. Pts	11	25	155	
Male	7 (64%)	18 (72%)	80 (52%)	0.139
Age at Transplant	56.9 (46-67)	55.4 (35.2-67)	56.1 (17-71)	0.685
BMI	24.7 (19.9-30.3)	26.5 (19.2-35.2)	26.2 (14.6-41.2)	0.588
Indication for Transplant (%)	IPF 5 (45%) COPD 5 (45%) Sarcoidosis 1 (9%)	IPF 16 (64%) COPD 8 (32%) Sarcoidosis 1 (4%)	IPF 74 (48%) COPD 45 (29%) Sarcoidosis 8 (5%) Other 28 (18%)	0.679

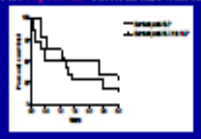
Kaplan Meier Median Survival: NLC vs No NLC



Kaplan Meier Plot of post-transplant Survival: NLC with NLP vs No NLC



Kaplan Meier Plot of post-NLP Survival: NLC with NLP vs No NLP



Characteristics of Native Lung Pneumonectomy Patients

Patient	Age	Sex	BMI	Indication for Transplant	Transplant Type	Prior Native Lung Thoracotomy	Pre- NLP Quantitative Perfusion
1	57	M	30.3	COPD	RSL	No	61.8% R 38.2% L
2	51	M	26.3	COPD	RSL	No	No study
3	60	F	27	IPF	LSL	Open lung biopsy	No study
4	54	F	26.3	Sarcoid	RSL	No	90.5% R 9.5% L
5	54	M	23.7	IPF	LSL	Open lung biopsy	5% R 95% L
6	61	F	21.2	COPD	RSL	No	86% R 14% L
7	57	M	26.3	IPF	LSL	VATS biopsy	No study
8	46	F	23.4	IPF	RSL	No	91% R 9% L
9	56	M	24.7	COPD	LSL	No	No study
10	60	M	19.9	COPD	LSL	No	9% R 91% L
11	57	M	22.9	IPF	RSL	No	No study

Need abbreviation list here

Outcomes Following Native Lung Pneumonectomy

Pt	Indication For NLP	MV Prior to NLP	Time from SLT to NLP	Post-NLP LOS	Post-NLP Complications	Post-NLP Survival	Survival Post-SLT	Cause of Death
1	NSCLC	No	336	5	None	139+	475+	N/A
2	Aspergilloma	Yes	40	59	Pneumonia Prolonged MV	1080+	1121+	N/A
3	Hemoptysis/ Aspergilloma	No	245	5	None	4+	250+	N/A
4	Hemoptysis/ Aspergilloma	No	496	5	None	102+	596+	N/A
5	Hemoptysis/ Aspergilloma	No	920	7	None	420+	1340+	N/A
6	BPF	No	719	7	None	858	1577	ROS/RF
7	BPF	Yes	80	44	Prolonged MV	117	197	RF/PNA
8	Recurrent Infection	No	2037	8	None	387	2424	ROS/RF
9	NSCLC	No	15	71	Pneumonia Prolonged MV	120	131	Tension PTX
10	NSCLC	No	1745	4	None	1142	2887	Metastatic NSCLC
11	NSCLC	No	11	8	AF	204	215	Metastatic NSCLC

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Impact of NLC on Survival

- Median time from transplant to major native lung complication was 1.28 years (0.04 to 5.1 years)
- Median survival for all SLT recipients during the study period was 5.1 years
- Median post-transplant survival was lower in SLT recipients with significant NLCs (3.9 years vs 5.3 years, p=0.004)
- No statistically significant difference in median survival between SLT recipients undergoing NLP as compared to SLT recipients without native lung complications (4.3 years versus 5.1 years, p=0.478)
- Trend toward improved post-transplant survival in SLT recipients with NLCs treated with NLP versus those not undergoing NLP (4.3 years versus 2.4 years, p=0.128)

NLP Outcomes

- All survived to discharge
- Median LOS post-NLP was 20.3 days (4-71 days)
- 4 of 11 (36% experienced complications)
  - Prolonged mechanical ventilation
  - Pneumonia
  - Atrial fibrillation

Limitations

- Small sample size precludes multivariate analysis comparing NLC and control groups
- Single institution study
- Causal link between decreased survival and NLC cannot be established
- Given retrospective nature, minor complications unlikely to be captured limiting study to "significant" NLC

Conclusions

- NLC are common and associated with worsened post-transplant survival
- NLC may explain some of the discrepancy in survival between SLT and BLT
- NLP is a reasonable therapeutic option for NLC with acceptable morbidity and mortality in select cases.

Prognosis Associated with Bronchiolitis Obliterans Syndrome Compared to Chronic Allograft Dysfunction Following Lung Transplantation

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Inova Advanced Lung Disease & Transplant Program

INTRODUCTION

- Lung transplantation may be complicated by chronic allograft dysfunction (CAD).
- One form of CAD is chronic allograft rejection which is manifest pathologically as Bronchiolitis Obliterans (BO).
- Bronchiolitis Obliterans Syndrome (BOS) is the physiologic surrogate which enables clinicians to make the presumptive diagnosis of chronic allograft rejection without subjecting patients to surgical lung biopsy.
- Therefore, BOS is a specific type of CAD that requires a permanent ≥ 20% decline in FEV_1 without evidence of an underlying cause such as a concomitant restrictive/infiltrative process.
- BOS portends a poor a prognosis but it is unknown whether the prognosis differs between patients with BOS and other forms of CAD.
- This study aims to compare these two groups with respect to mortality, lung function, and spirometric patterns.

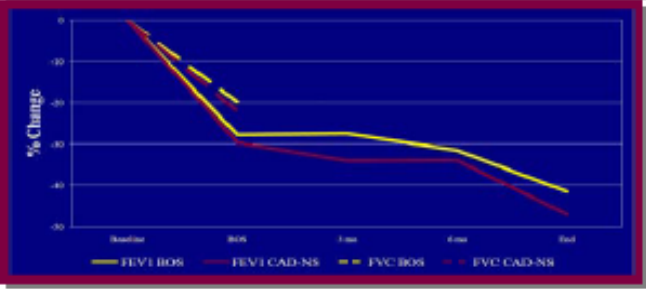
METHODS

- Single center retrospective review of all lung transplant recipients over a 12 year period.
- Abstracted variables include FVC, FEV_1, chest imaging, and all cause mortality. Spirometry data was collected from baseline, 3 & 6 months post transplant, and the last recorded pulmonary function test.
- CAD was broadly defined by a permanent ≥ 20% decline in post transplant baseline.
- First available chest imaging following CAD diagnosis was reviewed for the presence of allograft pleuroparenchymal infiltrates.
- Patients with radiographically clear chest imaging were labeled as BOS. All others were labeled CAD, Non-Specific (CAD-NS).
- Groups were compared with respect to mortality, decline in FEV_1, and FVC decrement at diagnosis.

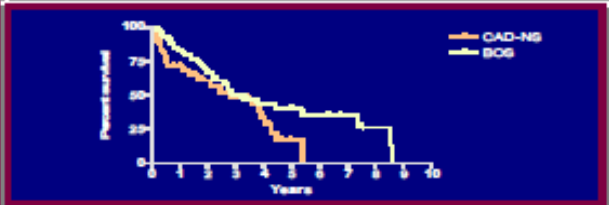
Baseline Characteristics

	BOS	CAD - NS	P value
Age	53.2	52.3	0.63
Male Gender	24 (42%)	21 (47%)	0.97
IPF	18 (35%)	19 (42%)	0.48
Sarcoid	4 (8%)	4 (9%)	0.85
COPD	18 (35%)	10 (22%)	0.15
Single Lung	41 (80%)	39 (87%)	0.41
Double Lung	10 (20%)	5 (11%)	0.41

Spirometry



Survival



Results

- At baseline we found no difference between groups with respect to demographics, type of lung transplant, or underlying pulmonary disease.
- We found no difference in mortality or subsequent decline in FEV_1 between patients with BOS and those with other non-specific forms of CAD.
- At the time of CAD diagnosis, the average decline in FVC from post transplant baseline was similar between groups.
- The proportion of patients with a ≥ 20% decline in FVC at diagnosis was also similar between groups.

Conclusion

- CAD which does not conform to the strict criteria of BOS is not uncommon in lung transplant recipients.
- The presence or absence of a radiographically defined concurrent restrictive process in lung transplant patients cannot be discerned by spirometric patterns.
- Radiographic infiltrates/ restriction may be a forme fruste of chronic allograft rejection or a distinct form of allograft injury.
- Whether pathologic BO accompanies radiographic infiltrates in patients with CAD remains to be determined.
- Establishing a rigorous diagnosis of BOS by ruling out a concurrent restrictive/infiltrative process does not appear to add any prognostic information to patients already meeting criteria for CAD.

NEUROSCIENCES PROGRAM

INOVA FAIRFAX HOSPITAL

Functional Pathway Mapping of Human Glioblastoma Multiforme (GBM) or WHO Grade IV Astrocytoma and Brain Metastases for Patient Tailored Therapy

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Abstract

Background: Genome scanning analysis of human glioblastoma multiforme (GBM) has suggested that this form of cancer is a protein pathway disease. Since genomic analysis cannot directly predict protein activation, analysis of protein pathway activation is required. With the current focus on targeted translational therapeutic modalities, a functional understanding of the GBM signaling repertoire is critical, and yet largely unknown.

Methods: Twelve tumors were included in this study: 10 GBMs (9 primary, 1 recurrent) and three brain metastases (2 breast and 1 lung). Pure tumor cell populations were obtained from fixed frozen tissue sections using Laser Capture Microdissection (LCM). Protein pathway mapping was performed using Reverse Phase Protein Microarrays (RPMA) whereby the activation of 85 key signaling proteins was quantitatively measured at once. Unsupervised and supervised analysis was used to explore pathway activation.

Results: Unsupervised hierarchical clustering of all tumors in the study set revealed largely patient-specific signaling portraits yet also identified distinct pathway subsets. The three metastatic tumors clustered separately and distinctly from the GBMs. The GBM specimens clustered according to pathway activity. Statistical analysis demonstrated significant correlations between certain phosphorylated endpoints detected and overall survival. Phosphorylation of cofilin (S3) was associated with shorter survival time, while Stat1 (Y701) and Shc (Y317) phosphorylation were both positively correlated with longer overall survival.

Conclusions: This study represents the most comprehensive proteomic analysis of human GBM pathway mapping to date. Since certain pathway biomarkers are themselves being targeted by current investigational therapies, the ability to map pathway activation and identify critical pathway biomarkers can lead to targeted therapeutics tailored to each patient's tumor. The ability to segregate short from long-term survivors according to protein pathway activation is promising.

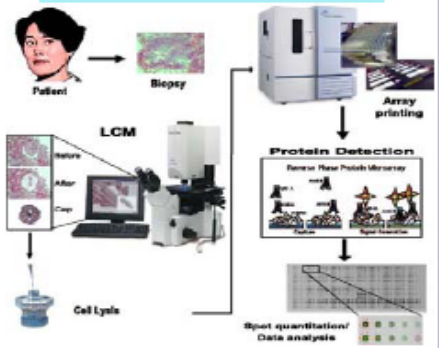
Introduction

- Current cancer therapy is directed to single targets while also being largely non-specific from a molecular perspective. Past efforts have focused on using gene transcript analysis and genome-wide mutational scanning to uncover drug targets and patient selection for better response. However, since transcription expression rarely correlates with protein expression, and even less so with post-translational modifications such as phosphorylation that drive signaling, in the near future, direct functional protein pathway information could be a more optimal biomarker repertoire for personalized therapy.

- We used a direct approach to elucidate activated protein signaling networks that would allow for the development of functional signaling maps for CNS cancers, even at the level of the individual patient.

- Direct functional pathway mapping of activated protein networks using Reverse Phase Protein Microarrays, could uncover new pathway biomarkers that can be used for patient stratification and developing molecularly targeted therapeutics.

Methods



- A patient's biopsy sample is subjected to LCM to isolate cells of interest under direct microscopic visualization.
- The microdissected cells are lysed in a buffer and rendered suitable for multiplexed protein pathway analysis using the Reverse Phase Protein Array (RPMA) platform.
- Cellular lysates are printed (spotted) onto a nitrocellulose coated slide using a robotic arrayer.
- Slides are incubated with a specific, validated antibody followed by an amplification and detection step.
- Spot intensities are calculated for further data analysis compared to controls and/or calibrators that are printed on the same slide.
- Arrays were scanned for spot intensity and data was normalized for each sample and used to explore pathway activation.
- Other statistical analyses demonstrated significant correlations between certain phosphorylated endpoints detected and overall patient survival.

Tumor Study Set

Sample Identifier	*Age at Diagnosis*	*Survival in days from Diagnosis*	*Diagnosis*	*Treatment*
M1	75	197	Lung Metastasis	Radiosurgery
M2	64	1053	Breast Metastasis	Chemotherapy, Whole Brain Radiotherapy Treatment, Radiosurgery
M3	61	762	GBM	Radiotherapy, Chemotherapy
M4	53	30	Breast Metastasis	Tumor resection
M5	47	350	GBM	Radiotherapy , Chemotherapy
M6	74	122	GBM	Radiotherapy
M7	60	255	GBM	Radiotherapy, Chemotherapy
M8	66	247	Recurrent GBM	Radiotherapy
M9	56	466	GBM	Radiotherapy, Chemotherapy
M10	84	66	GBM	No additional treatment
M11	64	956	GBM	Radiotherapy, Chemotherapy
M12	51	Alive	GBM	Radiotherapy, Chemotherapy

Table showing sample identifiers and some clinical data of the patients

Results

Phosphorylation/activation state of 67 key signaling proteins known to be involved in tumorigenesis and GBM activation, were determined by RPMA.

The results are shown in an activation map (below, Figure 1), which reveals clustering of EGFR, IGFR, AKT and mTOR networks for GBMs ,and HER2 pathway activation for one of the breast cancer metastasis (M2).

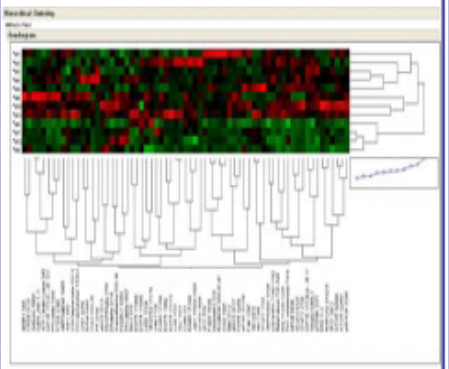


Figure 1: A heatmap generated by a hierarchical cluster analysis of phosphoproteins from 8 GBMs(M3,M5-M7,M9-M12),1 recurrent GBM (M8) and 3 metastasis [2 from breast (M2,M4) and 2 from lung (M1)] was used for reference. The patient tumor samples are shown on the vertical axis while the phosphoproteins of interest are shown on the horizontal axis. The colors shown represent relative protein level. Red represents high levels, black corresponds to intermediate, and green indicates a low level relative to other samples.

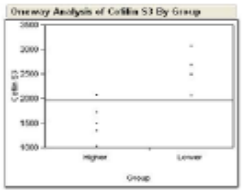


Figure 2: Analysis of phosphorylated Cofilin (S3) by higher or lower survival. Two separate groups are clearly identified where the increase in the level of Cofilin in the tumor samples is associated with lower survival.

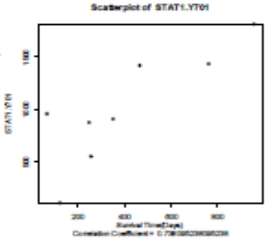


Figure 3: Analysis of STAT1 (Tyr701) phosphorylation versus survival time. STAT1 phosphorylation was positively correlated with longer overall survival ($r^2 = 0.738$).

Discussion

RPMA is a mature analytical method we originated for broad-scale multiplexed pathway activation mapping. Quantitative measurements of the activation of key signaling pathways (nodes) within clinical samples can serve as a basis for patient tailored therapy since these pathway analytes are the drug targets themselves. Understanding which pathways are activated and "in use" within the tumor for each patient will be critical for personalization of therapy. Molecular analysis of highly aggressive gliomas (GBM), as well as brain tumor metastasis has never before been performed using these pathway mapping tools. Pathway activation mapping revealed clustering of EGFR, IGFR, AKT and mTOR networks for GBMs. Brain metastases from breast and lung cancers appear distinct from GBM signaling in this study, indicating potential organ specific signaling.

In this study, we determined that increased levels of phosphorylated Cofilin (Ser3) were correlated with shorter survival while increased levels of phosphorylated STAT1 (Tyr701) were correlated with longer survival. **Cofilin** is a widely distributed intracellular actin-modulating protein that, when phosphorylated at Ser3, inhibits its actin depolymerization activity. More recent evidence supports a role of Cofilin in polymerizing actin, which influences the direction of cell migration, potentially increasing tumor metastatic potential. **STAT** gene expression is increased in many human cancers. STAT1, a transcription factor, can be considered a potential tumor suppressor, since it plays an important role in growth arrest and in promoting apoptosis. In this instance, STAT1 findings appear to support a role for increased phosphorylation levels as predicting better patient outcome.

Conclusions

- The identification of signaling activation maps from actual surgical biopsies is an essential step in achieving patient-tailored therapies, and this study demonstrates the feasibility of the RPMA, combined with LCM, to generate broad-scale pathway activation portraits for GBM and brain metastasis.
- Our study, while exploratory in nature, represents the most comprehensive protein signal pathway activation mapping ever performed for brain tumors and metastatic lesions.
- Activation of EGFR, IGFR, AKT-mTOR signaling networks appear to underpin a majority of our GBM study set.
- Activation portraits of brain metastases appear distinct from GBM.
- Specific pathway activation markers appear to correlate with survival.

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ORTHOPAEDIC RESEARCH PROGRAM

INOVA FAIRFAX HOSPITAL

Investigating the Fatigue Mechanism of Locked Plate Fixation of Proximal Humeral Fractures Using Acoustic Emission Technique

INOVA REGIONAL TRAUMA CENTER
Orthopedic Trauma Program

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INOVA FAIRFAX HOSPITAL

BACKGROUND

Proximal humeral fracture is a common bone fracture in elderly population. The fatigue properties of the bone-implant construct are critical to the success of the humeral fracture fixation. The fatigue-induced small cracks (fractures) can accumulate and propagate in bone and eventually coalesce into final failure. Previous research has mainly used interfragmentary rotation and displacement to investigate the fatigue mechanism of the fixation [1, 2], but none of them can detect the progression of bone crack activities that better indicate the procedure and causes of the fatigue failure.

OBJECTIVES

In this study we used acoustic emission (AE) technique [3] to monitor the microcrack activities in the entire fatigue procedure of the proximal humeral fractures fixed with the locked plate. We anticipated that AE technique can better reveal the failure mechanism of the humeral fracture fixation than the traditional mechanical tests.

MATERIAL & METHODS

- Ten humeri (5 matched pairs) were harvested. Proximal humeral fracture was created and fixed with a PERI-LOC® locked plate system (Smith & Nephew Inc. Memphis, TN).
- The specimens were subjected to cyclic compressive load of 500 N (±100 N) at 2 Hz for 15,000 cycles, or until gross failure when the actuator displacement reached 20 mm.
- 7 piezoelectric AE sensors (PAC, Princeton Junction, NJ) were glued onto the specimen to detect AE microcracks.
- Type I microcrack was an AE signal captured by four or more sensors, it was theoretically locatable in 3D. Type II microcrack (sensor number < 4) was unlocatable.
- The locations, amplitude and numbers of Type I and II microcracks were presented to demonstrate damage progression and severity.

Fig. 1 Mechanical testing setup (left) and AE sensors (right).

RESULTS

- Based on the failure cycles (Table 1), the specimens could be divided into three groups: the first included 3L and 3R, failed in less than 1,000 cycles. The second group had 1L, 2L, 1R, 2R and 4R, failed in less than 6,000 cycles. The third group had 4L, 5L and 5R, survived or failed around 15,000 cycles.
- Figure 2 indicated the displacements of actuator along fatigue of three samples from the three groups. The numbers of both Type I & II AE microcracks showed similar trend (Fig.3).
- The locations of Type I microcracks showed 1L, 1R had low amplitude microcracks accumulated around the middle and tip area of the screws until failure (Fig. 4A). Damage in both types was found jumping among screws in a spread pattern. 2R, 3L, 4R, 5L, 5R had few microcracks that was randomly distributed at the middle area (Fig. 4B)., 2L, 3R and 4L had high amplitude microcracks accumulated at the plate-screw interface area at first and lower amplitude microcracks at the middle and tip area (Fig. 4C and D).

Table 1. The results of mechanical and AE testing.

Specimen	1L	2L	3L	4L	5L	1R	2R	3R	4R	5R
Cycle No.	3118	5740	815	14514	15000	3687	2914	166	3356	15000
Disp. (mm)	20	20	20	20	5.41	20	15.3	20	13.2	7.63
Type I No.	99	313	15	67	1	51	9	108	4	17
Type II No.	2010	1817	213	398	65	1066	83	1150	101	104

Note: Disp. is actuator displacement; Cycle No. is failure cycle number.

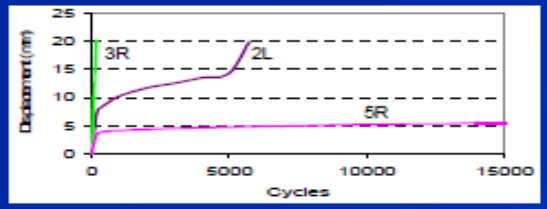

Fig.2. Actuator displacements of specimens 2L, 3R and 5R.

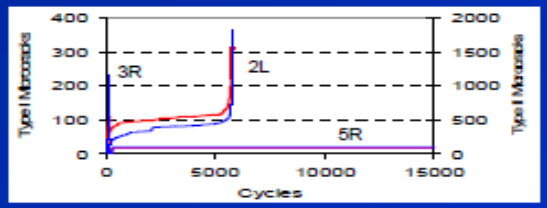

Fig.3. Number of Type I (red) and II (blue) microcracks of specimens 2L, 3R and 5R.

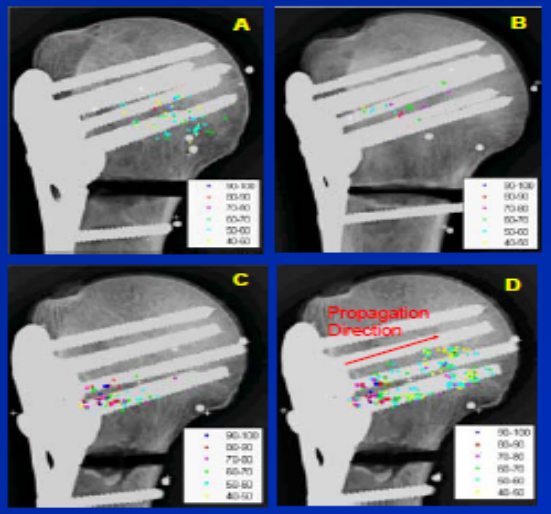

Fig.4. locations of Type I microcracks in 1L (A), 5R (B) and 2L (C shows the first 1000 cycles, D shows the entire test). Color legend shows the amplitude range of the microcracks.

DISCUSSION

The distribution and progression of the Type I microcracks showed that the damage in some failed specimens started from the screw-plate interface area, which is thought to have occurred in the local cortical bones. This suggested that cortical bones may be the first barrier to the failure and despite the increased strength of locking plate constructs, the point of failure still starts from the cortical bone. During the final failure period most microcracks occurred at the middle and tip area of the screws, suggested that the screw-cancellous bone interfaces is the final barrier. Any measure that can strengthen the interfaces, such as increasing the screw length, may improve the fatigue performances. The limitation of this study was the calculated locations of Type I microcracks were not very accurate due to the small size of the specimen and high velocity of AE signals [3]. As a result we were unable to correlate a Type I microcrack to a specific screw and identify its role in the fatigue failure of the humeral fracture fixation.

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Biomechanical Comparison of Two Ludloff Metatarsal Osteotomy Fixations: Compression Screws vs. Locking Plate

INOVA FAIRFAX HOSPITAL

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The Orthopaedic Foot & Ankle Center

BACKGROUND

Ludloff osteotomy fixation with compression screws has been widely used in the treatment of Hallux Valgus deformities [1, 2]. Generally six weeks of non-weight-bearing is required postoperatively to allow bony union. Besides the significant inconvenience due to non-weight-bearing, noncompliance may induce malunion, nonunion and loss of correction, indicating screw fixation is not strong enough for early weight-bearing. This scenario is worse when patients have poor bone quality [3]. The locking plate is a relatively new fixation method and is believed to have better mechanical stability with a potential of early weight-bearing and less correlation with bone quality. However, there is no study proving its advantages over the screw fixation.

OBJECTIVES

In this study, we investigated the biomechanical properties of a locking plate fixation and a compression screw fixation. The hypotheses were: 1. locking plate fixation is more mechanically stable than screw fixation; 2. locking plate fixation correlates less to bone mineral density (BMD) than screw fixation.

MATERIAL & METHODS

- Eight pairs of metatarsals were harvested and scanned using dual x-ray absorbitometry (DEXA) to quantify BMD.
- The proximal metatarsals were potted into PVC tubes using resin, then the Ludloff osteotomy was created.
- One metatarsal from each pair was randomly selected and fixed with two compression screws (Synthes Inc.), while the contralateral metatarsal was fixed with a locking plate system (Merete Medical Inc.).
- The specimens were fixed onto a MTS machine with the metatarsal angled 15 degrees plantarward (Fig. 1). The distal end of each specimen was subjected to cyclical compressive loading (0 to 70 N) at 0.5 Hz for 1,000 cycles or until gross failure. The specimens that survived were further loaded until failure. Paired t-tests were used to compare the mechanical stability (by mean of fatigue cycles) of the compression screws and the locking plate. Pearson tests were performed to examine the correlation between BMD and fatigue cycles of the two fixations.
- Four acoustic emission (AE) sensors were attached to the metatarsals to detect the elastic wave signals emitted from microcracks (small fractures) that occurred during the failure process. The time, number and linear location of the microcracks were determined to indicate the severity and progression of the fatigue damages in the fixations [4].

Figure 1: Experimental setup with four AE sensors attached on the specimen surface.

Table 1. Results of mechanical testing.

Specimen	Sex	Weight (lbs)	BMD (g/cm²)	Fixation method	Fatigue Cycles	Failure load (N)
1L	M	133	0.579	Plate	1000	203.1
1R	M	133	0.457	Screw	1000	147.3
2L	M	150	0.577	Plate	1000	179.6
2R	M	150	0.507	Screw	1000	122.7
3L	M	167	0.454	Screw	12	
3R	M	167	0.343	Plate	1000	130.4
4L	M	180	0.545	Plate	1000	196.4
4R	M	180	0.557	Screw	255	
5L	M	190	0.375	Screw	43	
5R	M	190	0.373	Plate	939	
6L	F	197	0.253	Plate	731	
6R	F	197	0.337	Screw	197	
7L	F	100	0.295	Screw	129	
7R	F	100	0.266	Plate	15	
8L	F	100	0.367	Plate	266	
8R	F	100	0.383	Screw	53	

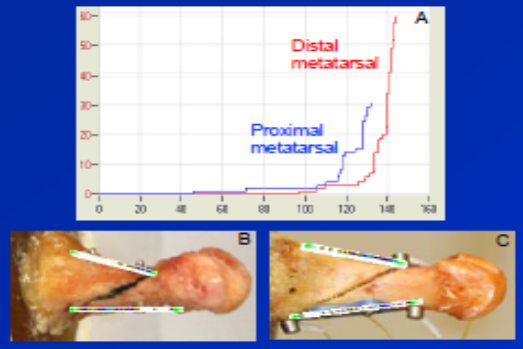

Fig 2. A: Microcrack number (Y axis) vs. time (X axis, in seconds) of a screw specimen. Blue line and red line represent the microcrack progression in the proximal and distal metatarsal. Microcracks' linear locations (color dots) on the proximal (top) and distal (bottom) metatarsal of screw (B) and plate (C) specimens.

RESULTS

- Four locking plate specimens and two screw specimens survived 1,000 cycles of fatigue testing. The average failure cycle of locking plate was 744, that of screw specimens was 336 (Table 1). The mechanical stability of plate fixation was significantly higher (p=0.034).
- The mechanical stability of both fixation methods positively correlated to BMD (screw fixation: correlation coefficient 0.469, p value 0.242; plate fixation: correlation coefficient 0.608, p value is 0.11), but not significant.
- The specimens fixed with screws failed catastrophically with dorsal angulation. The major reasons were loss of purchase of the distal screws and fracture of the dorsal cortex adjacent to the proximal screw. The failure mode of plate fixations was also dorsal angulation. The reasons included loss of screw purchase and distal metatarsal displacement. **The failure was not significant and recoverable when the load was removed**.
- AE results showed that microcracks occurred in screw fixations first at proximal metatarsal and then distal metatarsal (Fig. 2A). Their locations (Fig. 2B) indicated that the failure occurred from loss of distal screw purchase and followed by dorsal cortex fracture adjacent to the proximal screw. Microcracks in plate fixation started from the distal non-locking screw as well, then progressed to the distal metatarsal in a more spreading style, indicating the damages were not concentrated, or catastrophic. (Fig. 2C).

CONCLUSION/DISCUSSION

This study found that the Ludloff osteotomy fixed with a locking plate was much stronger than the traditional compression screw. The results, however, could not fully support the theory that the locking plate fixation is strong enough to eliminate a non-weight-bearing period. The author (SKN) however, has a clinical series of patients who were stabilized with the locking plate and allowed early weigh-bearing. At a follow-up of approximately 6 months, no failures have been seen. Based on the results of both clinical and biomechanical studies we are confident that the locking plate fixation is sufficient for early weight-bearing in patients with good bone quality. However, patients with low BMD should be very cautious for early weight-bearing. AE results indicated that the failure of both the locking plate and screw fixations started from the loss of distal screw purchase; this information may be useful to improve implant designs.

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The Influences of Screw Penetration Depth and Local Bone Quality to the Fatigue Failure of Locked Plate Fixation of Proximal Humeral Fracture

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BACKGROUND

The locked plate system that has rigid screw-plate interface is a relatively new method to fix displaced proximal humeral fractures. It was believed to have better initial stability and fixation strength over the traditional non-locked plate system in patients with poor bone quality [1]. However, previous biomechanical studies have had conflicting results on the relationship between bone mineral density (BMD) and the strength of the locked plate fixation [2, 3]. While BMD is an averaged bone quality of the central area of the humeral head, the strength of the fixation may better be determined by the specific region of the bones penetrated by the screws.

OBJECTIVES

We developed a new method that uses quantitative CT (QCT) to determine the path of each screw, quantify penetration depths, and apparent density of local cortical and cancellous bones. We hypothesized the mechanical strength of the locked plate fixation (by means of number of failure cycle) is influenced by the local bone quality (cortical density and cancellous density) and the screw penetration depth (cortical depth and cancellous depth).

MATERIAL & METHODS

- Ten humeri (5 matched pairs) were harvested and scanned using QCT with a calibration phantom containing K_2HPO_4.
- Proximal humeral fracture was created and fixed with PERI-LOC® locked plate (Smith & Nephew Inc.). The specimens were scanned using QCT post-operatively.
- Post-op QCT images were registered onto pre-op QCT images using Mimics (Materialise Inc.) (Fig. 1)
- BMD (equivalent to K_2HPO_4) of local bone along each screw's path was converted to apparent density (g/cm³) [5].
- Cortical depth (T_{cor}): sum of the penetration depth of all the screws in near cortex; cancellous depth (T_{can}): that in the cancellous bone. Cortical density (D_{cor}): averaged apparent density of all the screws of the local near cortex; cancellous density (D_{can}): that of local cancellous bone.
- The specimens were tested on a MTS frame (Fig.2) with cyclic compressive load of 500 N (±100 N) at 2 Hz for 15,000 cycles, or stopped when the displacement of MTS actuator reaches 20 mm.
- A nonlinear regression model was proposed among T_{cor}, T_{can}, D_{cor}, D_{can} and the number of failure cycle N:

$$\ln N = a\cdot T_{cor} + b\cdot D_{cor} + c\cdot T_{can} + d\cdot D_{can} + e\cdot T_{cor}^2 + f\cdot D_{cor}^2 + g\cdot T_{can}^2 + h\cdot D_{can}^2 + i$$

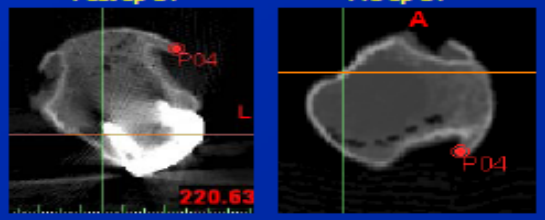

Figure 1: To register post-op CT onto Pre-op CT, three or more pairs of points (same location on the two CT sets, i.e. P04) need to be matched.

Figure 2: Mechanical testing setup.

RESULTS

- Only 2 specimens (5L and 5R) survived after 15,000 cycles of fatigue loading.
- Values for T_{cor}, T_{can}, D_{cor} and N showed a large variation among specimens, but not for D_{can} (Table 1).
- The equation was:

$$\ln N = 6.1064 D_{cor} + 0.5157 T_{can} + 56.0885 D_{can} - 0.0011 T_{can}^2 - 67.2296$$

- The number of failure cycle of the humeral fracture fixation was mainly influenced by D_{cor}, D_{can}, T_{can} and T_{can}^2 (Table 2). D_{can}'s influence is much more significant than D_{cor}. No significant influences were found for T_{cor} and other quadratic items.
- The residual (σ^2) of the regression model was 0.6411.

Table 1. The measured bone properties and failure cycles.

	Cortical Bone		Cancellous Bone		
Specimen	D_{cor} (g/cm³)	T_{cor} (mm)	D_{can} (g/cm³)	T_{can} (mm)	Cycle Number N
1L	0.42	9.95	0.17	241.29	3,118
2L	0.61	12.98	0.17	234.05	5,745
3L	0.71	15.11	0.18	305.86	815
4L	0.87	13.29	0.17	211.34	14,514
5L	0.67	10.09	0.18	267.35	15,000
1R	0.57	15.90	0.15	220.44	3,687
2R	0.51	11.22	0.18	224.87	2,914
3R	0.68	14.79	0.15	291.69	166
4R	0.71	11.31	0.17	211.67	3,356
5R	0.71	12.79	0.18	276.35	15,000

Table 2. The results of nonlinear regression model.

Parameter	Meaning	Unit	Coefficient	P-value
T_{cor}	Cortical Depth	mm	n.s.	
D_{cor}	Cortical Density	g/cm³	b=6.1064	0.0665
T_{can}	Cancellous Depth	mm	c=0.5157	0.0516
D_{can}	Cancellous Density	g/cm³	d=56.0885	0.0654
T_{cor}^2	Square of T_{cor}	mm²	n.s.	
D_{cor}^2	Square of D_{cor}	g²/cm⁶	n.s.	
T_{can}^2	Square of T_{can}	mm²	g=-0.0011	0.0448
D_{can}^2	Square of D_{can}	g²/cm⁶	n.s.	

Note: n.s. indicates that the parameter is not significant and excluded from the model

CONCLUSIONS

This study demonstrated that the screw penetration depth in the cancellous bone (cancellous depth) can be a significant predictor of the success of the humeral fracture fixation surgery using locked plate system. Although physicians can not control the bone quality of a patient, this study provided a method by which physicians can estimate an implant's performances based on projected screw paths and the patient's local bone quality. The limitation of this study was that the usage of the sum of penetration depth and averaged apparent density of all screws may ignore the important role of certain screws that may contribute more to the failure than others. However, conducting such a study will need more specimens and significantly increase the costs.

REFERENCES

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