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14. ABSTRACT

The "Translational Health – the Next Generation of Medicine" conference brought together scientists and medical professionals from across the country and Europe to present and discuss their research and clinical findings in all phases of biomolecular research including DNA sequencing, genotyping, expression analysis, protein separation and identification, and biomedical informatics analysis. This conference resulted in a greater understanding of human diseases and how through combining systems biology and high-throughput molecular analysis can improve patient care in both the military and civilian sectors.

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Table of Contents

INTRODUCTION

The Windber Research Institute is a private, nonprofit biomedical research institute that, through a unique partnership with Walter Reed Army Medical Center, is focused on the issues of women's health, cardiovascular disease, the metabolic syndrome and the process of aging that adversely affect the military and civilian populations of this country. Its mission to promote translational medicine in order to move research questions and findings from the bedside to the bench as well as from the bench to the bedside by expanding existing knowledge, employing new technologies and conducting original discovery research. The genomics, proteomics and biomedical informatics communities have a wealth of experience in producing and using information generated within their respective domains. The successful movement of genomics and proteomics information into the clinic can be significantly accelerated with platforms that are standardized and research informatics seamlessly linked to medical informatics. This can be achieved through collaboration among clinicians and scientists to bridge existing gaps among disciplines, improving and standardizing the methods used in data collection, and efficiently managing the storage, analysis and retrieval of the massive amount of data generated from new large-scale experimental techniques such as microarray gene expression profiling and mass spectrometry. The challenge associated with the generation of massive amounts of molecular information using automated systems and linkage genotype and phenotype information offers strong opportunities for public/private collaboration. Making this linkage is a key step in linking biologically and clinically useful information, elucidating biochemical pathways, stratifying disease, understanding the mechanism of known drugs, discovering new drugs and moving scientific discoveries into the clinical rapidly.

The conference "Translational Health – the Next Generation of Medicine" focused on how combining systems biology and high-throughput molecular analysis impact our understanding of human disease and how this understanding can be translated into improved quality of patient care. A wide range of scientists and medical professionals from the U.S. and Europe addressed technology developments and diverse disease areas including, but not limited to breast cancer, cardiovascular disease and childhood obesity. The conference Keynote Speaker was Dr. Leroy Hood, President of the Institute for Systems Biology. Recently, Dr. Hood was awarded the prestigious 2004 Association for Molecular Pathology (AMP) Award for Excellence in Molecular Diagnostics. He also received the 2003 Lemelson-MIT Prize for Innovation and Invention, the 2002 Kyoto Prize in Advanced Technology and the 1987 Lasker Prize for his studies on the mechanism of immune diversity. He is a member of the National Academy of Sciences, the American Philosophical Society, the American Association of Arts and Sciences, and the Institute of Medicine. Dr. Hood has also played a role in founding numerous biotechnology companies, including Amgen, Applied Biosystems, Systemix, Darwin and Rosetta.

Dr. Hood and Mr. CC Clyburn, Telemedicine & Advanced Technology Research Center, facilitated a networking meeting in which attendees had the opportunity to discuss their research interests and assess prospects for potential collaborations with WRI and other attendees. Dr. Hood opened the networking meeting by sharing his insights on the key success factors required for pioneers at the intersection of molecular biology, economics and society.

BODY

The "Translational Health – the Next Generation of Medicine" conference brought together scientists and medical professionals from across the country and Europe to present and discuss their research and clinical findings in all phases of biomolecular research including DNA sequencing, genotyping, expression analysis, protein separation and identification, and biomedical informatics analysis. This conference resulted in a greater understanding of human diseases and how through combining systems biology and high-throughput molecular analysis can improve patient care in both the military and civilian sectors. The presentation and poster abstracts with presenter biographies follow.

PRESENTATIONS

Systems Medicine of the Future: Predictive, Preventive, Personalized and Participatory

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Abstract

Medicine will be profoundly changed by new systems approaches to disease. I will discuss what systems biology is, why the informational view of biology is central to this approach and what systems medicine is--using prion infection in mice as a model. I will then discuss how this view of systems medicine together with new technologies for in vitro and in vivo measurements push us towards a medicine that is predictive, preventive, personalized and participatory.

Biography

Dr. Hood's research has focused on fundamental biology (immunity, evolution, genomics), systems medicine (prostate cancer and prion disease) and on bringing engineering to biology through the development of five instruments—the DNA and protein sequencers and synthesizers and the ink-jet oligonucleotide synthesizer-- for deciphering the various types of biological information (DNA, RNA, proteins and systems). These instruments and their subsequent improvements constitute the technological foundation for modern molecular biology and genomics. Dr. Hood has applied these technologies to diverse fields including immunology, neurobiology, cancer biology, molecular evolution and systems biology and medicine. Dr. Hood has been driven by the convection that the needs of frontier biology should drive the choice of technologies to be developed and once a new technology is developed these technologies can revolutionize biology and medicine. His professional career began at Caltech where he was one of the pioneers in the field of molecular immunology and he catalyzed the development of four instruments—the DNA gene sequencer and synthesizer, and the protein synthesizer and sequencer. He founded Applied Biosystems to commercialize these instruments. In particular, the DNA sequencer has revolutionized genomics by allowing the rapid automated sequencing of DNA, which played the crucial role in contributing to the successful mapping of the human genome during the 1990s. He applied all of these technologies to the study of molecular immunology (and discovered many of the fundamental mechanisms for antibody diversity) and neurobiology (he cured in mice the first neurological disease by gene transfer). In 1992, Dr. Hood moved to the University of Washington as founder and Chairman of the cross-disciplinary Department of Molecular Biotechnology (MBT). Here he developed the ink-jet oligonucleotide synthesizer to synthesize DNA chips and permit the simultaneous analyses of all 25,000 human genes. Agilent has commercialized this technology. At MBT he applied all of the technologies that he developed to the study of cancer biology and prion disease from a systems vantage point. In 2000, he co-founded the Institute for Systems Biology in Seattle, Washington to more effectively continuing pioneer systems approaches to biology and medicine. Here he has contributed seminal papers to delineating the systems approach to biology and disease and to pioneer developing new technologies (microfluidics/nanotechnology and molecular imaging) in collaboration with colleagues at Caltech and UCLA that are establishing the framework for medicine evolving from its current reactive mode to a predictive, preventive, personalized and participatory modes (P4 medicine) over the next 5-20 years. Dr. Hood was awarded in 1987 Lasker Prize for his studies on the mechanism of immune diversity. Dr. Hood was also awarded the 2002 Kyoto Prize in Advanced Technology for the development of the five different instruments. He received the 2003 Lemelson–MIT Prize for Innovation and Invention—for the development of the DNA sequencer. Most recently, Dr. Hood's lifelong contributions to biotechnology have earned him the prestigious 2004 Biotechnology Heritage Award and his pioneering efforts in molecular diagnostics the Association for Molecular Pathology (AMP)

Award for Excellence in Molecular Diagnostics. Dr. Hood has received 14 honorary degrees from Institutions such as Johns Hopkins, UCLA, and Whitman College.

He has published more than 600 peer-reviewed papers, received 14 patents, and has co-authored textbooks in biochemistry, immunology, molecular biology, and genetics, and is just finishing a textbook on systems biology.

He is a member of the National Academy of Sciences, the American Philosophical Society, the American Association of Arts and Sciences, and the Institute of Medicine. Dr. Hood has also played a role in founding more than 14 biotechnology companies, including Amgen, Applied Biosystems, Systemix, Darwin and Rosetta. He is currently pioneering systems medicine and the systems thinking for diagnostics, therapy and ultimately prevention.

Systems Biology in Diagnostic Applications – Finding the Needles in the Haystack for Early Detection of Cancer

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Abstract
Our research employs a radically simplified approach to the discovery of serum biomarkers. The combination of transcriptomic and proteomic analyses with advanced informatics techniques and algorithms allows for highly selective prediction of organ-specific biomarkers. This powerful approach allows for a reduction of protein complexity in serum prior to proteomic analysis. We are developing a broad panel of biomarker assays initially focusing on prostate and breast cancers. Our aim is to enable patients to be screened regularly and cost-efficiently for a broad array of the most common diseases by providing nothing more than a blood sample for analysis. Such simplified approaches facilitate early intervention in a variety of diseases and will allow accurate predictions as to appropriate courses of treatment. Leveraging these technologies in combination represents a significant step toward understanding disease onset and progression.

Biography
Dr. Patricia Beckmann joined Homestead Clinical Corporation as the founding Chief Scientific Officer in 2005. Homestead was founded to commercialize a suite of technologies developed in Lee Hood's and Ruedi Aebersold's laboratories at the Institute for Systems Biology (ISB). Homestead's goal is to develop diagnostic /prognostic/theranostic tools, designed to facilitate early intervention in a variety of diseases and to make accurate predictions as to appropriate courses of treatment.

Prior to Homestead, Dr. Beckmann was responsible for biotechnology venture investment opportunities at Vulcan Capital. Vulcan is a private investment group founded by Microsoft co-founder Paul G. Allen to manage his personal and professional endeavors.

Previous to Vulcan, she held various research and management positions at Immunex Corporation and Amgen. Dr. Beckmann was named National Inventor of the Year in 2001 for her research discovering TNF receptor molecules (now marketed as Enbrel for patients with rheumatoid arthritis). Most recently at Amgen, she was a liaison in research administration and law and was responsible for extramural collaborations, intellectual property and technology assessments.

Dr. Beckmann is a Kauffman Fellow at Accelerator Corporation and is active mentoring students and entrepreneurs as an Expert-in-Residence at the University of Washington, School of Business. She also served as director of a privately held real-estate development corporation, and in a similar capacity for other not-for-profit community development organizations.

She holds a Ph.D. in biochemistry and pharmacology from the University of Arizona, School of Medicine and a B.A. degree in biology, chemistry and art from The Evergreen State College in Washington State.

She pursued postgraduate studies as a Fulbright Scholar at the Ludwig Institute at Uppsala University, Sweden, and as a Visiting Scientist at the National Cancer Institute in Bethesda, Maryland. Patricia has over 50 scientific publications and more than thirty issued US patents.

Building an Infrastructure for Translational Research

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Abstract
The rapidly evolving field of translational research presents a number of significant IT challenges. Among these, the effective management of vast quantities of data being generated from both clinical trials and clinical practice has become increasingly important.

Biography
Prof. Yike Guo founded InforSense in November 1999 to commercialize his group's pioneering Open Discovery Workflow technology for high-performance large-scale integrative data analysis, rapid application building and process knowledge management. He has led the company's growth since then. He is a world leading expert in large scale data mining and Grid computing and also serves as Technical Director of the Parallel Computing Center and Head of the Data Mining Group at Imperial College, University of London. Over the last four years he has led a number of significant academic and industrial research and development projects targeted at building next generation e-Science platforms for which he has gained UK and European funding in excess of Ł10million. He holds a PhD in Computing Science from Imperial College.

Stress: Individualized Genomic Expression

Barry Bittman, MD
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Adjunct Research Investigator – Windber Research Institute
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Abstract
Dr. Bittman presents a series of key insights and findings from a recently published scientific investigation that documented individualized genomic stress induction signatures and their reversal through a unique recreational music making protocol. He discusses current collaborative research with WRI that focuses on stress biology and genomic signatures in the context of disease management. Dr. Bittman concludes with perspectives for integrating genomic assessment into strategic algorithms for enhancing patient outcomes.

Biography
Barry Bittman, MD is a neurologist, author, international speaker, award-winning producer/director and inventor. As CEO and Medical Director of the Mind-Body Wellness Center, a comprehensive, interdisciplinary outpatient medical facility in Meadville, PA., Dr. Bittman has pioneered a new paradigm for treating the "whole person." Based upon extensive research, he developed Insights for Living Beyond Cancer with Bernie Siegel, MD, a program that integrates the power of mind, body and spirit with conventional medical care. Dr. Bittman has also created similar programs for individuals facing the challenges of asthma, cardiovascular disease, chronic lung disease and diabetes.

As the host of the first nationally-syndicated integrative medicine weekly Public Radio program, Mind-Body Matters, Dr. Bittman interviewed 115 of the world's leading visionaries. His program featured cutting-edge in-depth perspectives that scientifically substantiate the integration of complementary approaches into conventional healthcare. Dr. Bittman's more than 250 articles on a host of integrative medical topics have been published in his newspaper column, Mind Over Matter.

Dr. Bittman's latest research, a 2-phase study demonstrated for the first time that playing a musical instrument reverses multiple elements of the human stress response on the genomic level (*Medical Science Monitor* Feb. 2005). His team included researchers from Loma Linda University School of Medicine and Applied Biosystems, the developer of the original technology that led to the successful mapping of the human genome announced in June, 2000. Stress-reduction was far greater for individuals participating in their first group keyboard lesson (Yamaha's Clavinova Connection) than for subjects who simply relaxed and read newspapers and magazines. In addition, the researchers introduced the concept of *individualized genomic stress induction signatures,* which uniquely demonstrate biological diversity in action.

Minimally Invasive Surgery (CME)

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Abstract
The objectives of this presentation are:
At the conclusion of this learning activity, the participant should be able to:

1) Review the general benefits of MIS.
2) Review surgical procedures amenable to MIS
3) Review the results of MIS procedures

Biography
Dr. Marley has been in the practice of General and Advanced Laparoscopic Surgery since 1992. He retired from the United States Army in 2005, after 21 years of service. Dr Marley was on the teaching staff at Walter Reed Medical Center for his last 10 years of service. He was the Chief of Minimally Invasive Surgery and Bariatric Surgery when he retired.

Here at Windber Medical Center, he continues to practice general surgery, specializing in Minimally Invasive Surgery. Dr Marley specializes in laparoscopic procedures such as cholecystectomy, hernia repair, Nissen Fundoplication, colon resection, splenectomy, appendectomy, adrenolectomy and weight loss surgery.

Dr. Marley also performs standard surgical procedures, as well as colonoscopies, EGD's and PEG's. He is also on call to provide emergency (unscheduled) general surgical services, such as for acute appendicitis or bowel perforations, whenever they might be needed.

Dr. Marley graduated from Wayne State University School of Medicine, Detroit, Michigan in 1983. He did his internship at Wilford Hall USAF Medical Center and his General Surgical residency training at Dwight David Eisenhower Army Medical Center. He was certified in General surgery by the American Board of Surgery in 1993 and recertified in 2002.

Integrin Profiling: Diagnostic and Therapeutic Opportunities

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Abstract
In cancer, integrins are involved in loss of anchorage-dependent growth, tumor angiogenesis and tumor cell migration during tissue invasion and metastasis. Integrin functions are important in nearly every tissue and knowledge is far from complete. Cells usually express more than one integrin, in complex patterns that can change with time and environment and overlap between cell types. Because some integrins are upregulated in both invasive cancer cells and angiogenic endothelial cells, their targeting might confer a significant therapeutic advantage. Immunohistochemical profiling of the integrins provides helpful information for the selection of candidates for these clinical trials.

Biography
Al is the President and CSO of **MDR** (**M**olecular **D**etection and **R**etrieval) Global Systems, LLC located in Windber, PA. He also provides consultative services in cellular analysis including immunohistochemistry (IHC), flow cytometry and molecular biology for the Windber Research Institute (www.wriwindber.org). Previously Al held a pathology faculty position as Technical Director of Immunopathology, Flow Cytometry and the University Tumor Bank at Thomas Jefferson University Hospital in Philadelphia, PA.

Al is a board member of the Society for Applied Immunohistochemistry (www.apliedimmuno.org), where he promotes the standardization of IHC reagents and their application. In the field of immunohistochemistry, Al is considered to be the leading authority on the application and utilization of automated antigen detection systems. Al has co-authored more than 100 articles and abstracts applying immunohistochemistry in diagnostic surgical pathology. Al has been an invited speaker at numerous meetings for technologists, scientists and pathologists.

Data Warehouse for Translational Research

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Abstract
The goal of the WRI data warehouse is to provide data and analytical support to institute's translational research. To this end, in collaboration with InforSense and Concentia Digital, an On-Line Analytical Processing (OLAP) tool has been developed to allow for easy access and stratification of hundreds of data elements across thousands of subjects enrolled in the Clinical Breast Care Project (CBCP). A 'patient view' tool has been developed to allow for exploration of warehoused data from an individual patient. An application prototype has been developed to enable users to access clinical or experimental images at ease with a built-in robust data-element filtering capability. All these translational research-enabling applications will be migrated to and further developed on a newly designed patient-centric, object-oriented data model with a temporal dimension. We expect that this newly designed data model, which is in the process of being implemented, will dramatically enhance our translational research capability when compared to the old questionnaire-based data structure. In this presentation, I will also discuss the handling of protected health information, and I will describe a couple of research projects using this data warehouse.

Biography
Dr. Hai Hu is currently Sr. Director of Biomedical Informatics at Windber Research Institute, leading the development of the biomedical informatics infrastructure and heading several research projects. He has many years of direct experiences applying computational and statistical technologies to solving high-throughput biological problems, including the development of data mining and data analysis tools, and data tracking systems. Before moving to Windber he held the position of Group Leader and Sr. Bioinformatics Scientist at AxCell Biosciences. Preceding this he conducted research as a molecular biophysicist/biologist for 4 years after obtaining his PhD. His educational background includes physics (BS), speech recognition/computer engineering (MS), statistics (MS program), and biophysics (PhD). He is often invited to national and international scientific and business conferences for presentations, and sometimes functioning as bioinformatics program chair or session chair. He is a reviewer for a number of journals including *Bioinformatics* and *Proteomics*.

A Novel Anti-Invasion Therapy for Aggressive Cancers

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Abstract
Tumor invasion and metastasis require breakdown of the stroma, which is accomplished by Matrix Metalloproteinase-1 (MMP-1), an interstitial collagenase with the singular ability to degrade stromal collagen types I and III. MMP-1 has a central role in cancer because a single nucleotide polymorphism in its promoter ("2G allele") increases expression of this enzyme through an ETS site. Since high levels of MMP-1 are linked to metastasis and poor patient outcome, inhibiting MMP-1 is an attractive therapeutic goal.

We used RNAi technology with MMP-1 shRNAs stably transfected into VMM12 melanoma cells and MDA-231 breast cancer cells to specifically inhibit MMP-1, and to demonstrate proof-of-principle that blocking MMP-1 was therapeutically effective.

Compared to tumor cells with a control vector, melanoma and breast cancer cells expressing MMP-1 shRNAs showed > 90% decrease in MMP-1 mRNA and protein, and failed to degrade type I collagen *in vitro*. Orthotopic (intradermal) injection of melanoma cells expressing either a control or MMP-1 shRNA into nude mice gave rise to primary tumors of equal size. However, melanoma cells with the control shRNA metastasized to the lung while cells harboring the MMP-1 shRNA did not. In contrast, when breast cancer cells harboring the MMP-1 shRNA were injected orthotopically (mammary fat pad) into nude mice, the primary tumors were significantly (P= 0.027) smaller than control tumors, demonstrating reduced growth of primary breast tumors. We conclude that blocking MMP-1 expression blocks tumor growth and/or metastasis, and we propose that exogenously administered siRNAs represent a promising new therapeutic strategy to reduce tumor progression.

Biography
Constance E. Brinckerhoff, PhD is the Nathan Smith Professor of Medicine and of Biochemistry at Dartmouth Medical School. Dr. Brinckerhoff also serves as Associate Dean for Science Education at the Medical School and as the Director of the MD/PhD Program. Dr. Brinckerhoff has been a member of several editorial boards, including *Arthritis and Rheumatism* and the *Journal of Biological Chemistry*, and she is currently an executive editor of the *Journal of Cellular Physiology*. She has served two terms on the Pathobiological Chemistry Study Section at NIH, as well as on the NIH Recombinant DNA Advisory Committee. Dr. Brinckerhoff holds her undergraduate degree from Smith College and her doctorate in microbiology from the School of Medicine, SUNY at Buffalo. Her research focuses on the role of Matrix Metalloproteinases in joint destruction in arthritis and in tumor invasion and metastasis.

Integrated Information Technology and Biocomputing Infrastructure for Pancreatic Cancer Collaborative Research

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Abstract

We have developed a web-based Integrated Information Technology and Biocomputing Infrastructure (IITBI) for pancreatic cancer (PC) collaborative research. IITBI allows researchers from multiple centers around the world to collect a variety of critical information and biospecimen data on PC patients and high-risk subjects in a standard and efficient way, as well as to mine the collected data and perform sophisticated data analysis. The IITBI contains three integrated components: (1) the PC Collaborative Registry (PCCR) to gather standardized PC data from multiple centers; (2) the PC Data Warehouse to mine this data; and (3) the PC Statistical Modeling to perform statistical analysis and prediction. Each user has an appropriate level of access to the data. All subjects' Protected Health Information collected in the PCCR is encrypted when entered into the database. The PCCR maintains an audit trail of all data entries to protect the authenticity, integrity and confidentiality of the data. The application is accessible to participating sites. At present, seven cancer centers utilize this system. As of July 2006, the PCCR contains data on 1,239 subjects. Data collected in the PCCR is being used as a platform for several research projects, which should lead to a better understanding and treatment of PC.

Biography

Dr. Sherman received his M.S. degree in Mathematics and Physics in 1970 from Byelorussian State University and his Ph.D. in Biophysics in 1978 from the Institute of Physics, Academy of Sciences of the USSR. Dr. Sherman has more than 100 publications related to the application of computational methods in biomedical research. He holds several U.S. patents. Dr. Sherman was recently awarded a $1.5 million grant to develop biomedical computing tools for pancreatic cancer research. Dr. Sherman has been the P.I. or Co-investigator of seven NIH grants; four NE Department of Health grants; two NRI grants; and an EPSCoR NSF grant. He has served as a member of many *ad hoc* committees to review grant applications submitted to the NIH. Dr. Sherman has served on a number of advisory committees for Ph.D. and M.S. students at the University of Nebraska Medical Center (UNMC), the University of Nebraska-Omaha and Creighton University. He represents the UNMC Eppley Institute for Research in Caner in the caBIG activities of the NCI and is a member of the Clinical Trials Management Systems Workspace. Dr. Sherman is a member of the Editorial Board of the journal "Cancer Informatics".

The Clinical Breast Care Project: An Important Resource in Investigating Environmental and Genetic Contributions to Breast Cancer in African American Women.

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Abstract

Age at diagnosis, pathological characteristics, and tumor behavior differ between African American (AAW) and Caucasian women (CW) with breast cancer, with AAW having more aggressive tumors and higher mortality rates. Although both societal and molecular contributions to these disparities have been suggested, the African American population has traditionally been under-represented in tumor registries and clinical protocols, limiting the power of epidemiologic and molecular studies to provide better understanding of disease pathogenesis in this minority population.

The Clinical Breast Care Project (CBCP) has developed a large tissue and blood repository from patients undergoing treatment for breast cancer, with previous history of breast cancer, counseled in the Risk Reduction Clinic, screened by routine mammography, or undergoing elective reductive mammoplasty.

The success rate for recruitment of AAW was high; 24% of the 2,209 patients were African American, including 15% disease-free, 12% high-risk, 54% benign, 6% preinvasive and 13% with invasive breast disease. More than 500 data fields regarding lifestyle choices, socioeconomic status, health history and geography were collected from all participants, and all consenting individuals provided blood specimens for genomic and proteomic studies. Tissues

Biography
Rachel Ellsworth received her PhD in biomedical sciences from the University of Texas, Health Science Center, Houston. Her postdoctoral training took place at the NIH where she worked on the human genome project. In 2001, Dr. Ellsworth moved to the Windber Research Institute, which serves as the research arm of the Clinical Breast Care Project.

Much of her early work focused on the identification of chromosomal regions critical to the development, progression and metastasis of primary breast tumors. In 2004, Dr. Ellsworth, in collaboration with Dr. Henry Lynch, was awarded a grant from the Susan G. Komen Breast Cancer Foundation for her project "Identification of novel genetic factors contributing to clinical phenotypes in large families with BRCA1 and BRCA2 mutations". Her current grant is entitled “Development of biological models to differentiate aggressive from indolent DCIS” will identify genes involved in determining the underlying behavior of DCIS lesions. This work will move the diagnosis and classification of DCIS beyond current pathological standards and allow for women with preinvasive breast disease to receive the appropriate, customized treatments.

Translational Cardiovascular Health

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Abstract

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Translational cardiovascular health is the application of evidence-based interventions in order to achieve the best sustained level of circulatory fitness that an individual’s genetic endowment, life situation and human relationships can support. Our research examines intensive lifestyle interventions at the functional and molecular level in order to expand and validate the evidence base that informs these personal decisions. Our participants are fully engaged in understanding, carrying out, and learning from their life choices.

Our ability to measure expression of the genetically driven risk factors that promote coronary artery plaque formation and progression, for example, LDL cholesterol, diabetes, and the metabolic syndrome, is reaching a level that allows general conclusions on the value of interventions to minimize risk. We also have new imaging methods to determine the effect of intervention on progression, stabilization and reversal of atherosclerosis. Improvements in life choices such as physical activity, diet, and stress management appear to have greater benefit

than specific medical therapies, which are also needed in virtually all persons at risk. We still lack the capacity to predict the impact of specific interventions that in the future will be tailored to the genetic background and life situations of individuals.

Lifetime sustainment of a beneficial translational health change requires strong personal confidence in its value. Patients who take ownership of their own health information and take charge of their health choices in partnership with supportive providers and patient focused information systems will gain the confidence they need to be successful.

Biography

Michael A. Dunn, MD, FACP is Chief Medical Officer of Windber Research Institute. He directs its Integrated Cardiac and Metabolic Health Program. His work in outcomes-focused preventive care and electronic health record support of cardiovascular and metabolic risk reduction in military health was recognized at the US Institute of Medicine's first Quality Chasm Summit.

Dr. Dunn is a Professor of Medicine and Preventive Medicine/Biometrics at Uniformed Services University of the Health Sciences, and commanded the Walter Reed Health Care System and the Army's health facilities in the western US, retiring as a Brigadier General. He serves as a Senior Medical Advisor for Public Health Emergency Medical Countermeasures for the US Department of Health and Human Services.

Obesity Induced Changed in the Liver

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Abstract

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In healthy individuals, adipose and liver interact to control lipid homeostasis. Consumption of fructose, a commonly used sweetener, is associated with insulin resistance and hyperlipidemia in humans as well as animal models. High fructose consumption is linked to onset of obesity and deregulation of lipid metabolism. As a result, triglycerides are stored in non-adipose tissue, including liver. The appearance of fatty liver is associated with elevated, circulating free fatty acids and triglycerides as well as development of diabetes. Physiologic and proteomic, as well as immunohistochemistry-based, examination of liver and serum from high fructose-fed hamsters have been employed to elucidate the molecular mechanism linking fructose consumption to development of diabetes and impaired lipid metabolism. The study design involved nutritional intervention by feeding hamsters 1) high fructose diet; 2) high fructose diet followed by treatment with Fenofibrate (a commonly used anti-hypertriglyceridemia agent); and 3) comparison with a control group raised on regular chow. Following dietary intervention, blood glucose, insulin, and lipid profiles were determined along with evaluation of liver histology as well as total liver proteomics. Hamsters fed high fructose diet, as opposed to animals treated with Fenofibrate as well as control animals raised on regular chow, exhibited hyperinsulinemia, impaired glucose tolerance, elevated plasma lipid levels, and fat infiltration in the liver. MALDI-based proteomics identified differentially expressed proteins, including proteins linked to fructose catabolism as well as lipid and cholesterol metabolism. Preliminary data have provided insight into the underlying mechanism of fructose-induced fatty liver and insulin resistance.

Biography
Steven Ringquist is an Assistant Professor at Children's Hospital of Pittsburgh. He has authored 24 original research papers and 7 review articles. Dr. Ringquist received bachelor degrees in Chemistry and Biology from California State University (class of 1982) and a doctorate degree in Biological Chemistry from the University of Illinois (class of 1987).

He went on to study in the field of genomics with Charles Cantor at Columbia University (1988-1989) where he mapped epigenetic changes occurring in genomic DNA. Later he worked with Larry Gold at the University of Colorado (1990-1993) on developing computational models for measuring the influence of RNA elements that control gene expression. In 1994 he accepted a position as Senior Scientist at Nexstar Pharmaceuticals where his work on modulators of protein activity resulted in the awarding of 5 U.S. Patents. In 1997 Dr. Ringquist was promoted to Principal Scientist for drug discovery. He returned to academia by obtaining a fellowship at the Sidney Kimmel Cancer Center where he investigated changes in expression of low copy number mRNA from tumor cells (1998-2000). In 2001 he moved to his current position at Children's Hospital of Pittsburgh. Dr. Ringquist's research combines computational, genetic, and proteomic tools for the identification of molecular markers that predict the risk of developing childhood diabetes and its complications. He is a member of the American Association for the Advancement of Science and has served on the National Cancer Institute study section for Innovative Technologies for the Molecular Analysis of Cancer. His research is supported by funds from the NIH Autoimmunity Centers of Excellence and the Department of Defense Telemedicine and Advanced Technology Research Center.

Translational Pediatrics in School Based Obesity Intervention

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Abstract
Objectives: The role and activities of a Health Promoting Hospital will be defined. We will also define the issue of obesity as it relates to Translational Medicine with a final comment on the potential benefit of translational medicine in a community setting.

Methods: A brief history of the development of a Health Promoting Hospital in a U.S. health care system will be offered with an emphasis on the monitoring and evaluation of community based health promotion/disease prevention programs. The speaker will then present a short review of the literature demonstrating the benefit of a co-existence between translational medicine and obesity related public health initiatives in a community setting. A review of the obesity and fitness HP/DP programs implemented, coordinated, monitored and evaluated by a regional health care system will also be presented.

Discussion: The discussion will hopefully entail lively debate regarding the role of a community hospital as a health promoting hospital and the possibilities of incorporating translational medicine as a health promoting partner in addressing the obesity epidemic.

Biography

Education: Dr. Masiello completed his pediatric residency at Bridgeport Hospital in Bridgeport, CT and fellowship in pediatric critical care medicine at Harvard University, Boston's Children's Hospital. He received his Masters in Public Health from the George Washington University School of Public Health and Health Services in Washington, DC.

Positions: Vice-President, Conemaugh Health System and Director of the Office of Community Health Dr. Masiello and his staff have been able to develop health promotion/disease prevention programs for this rural, economically depressed region. Dr. Masiello is Medical Director for The Laurel Highlands Clinic for Children with Special Needs. Prior to this position, he held positions as medical director of pediatric intensive care units.

Recognition: In 1995-96, Dr. Masiello received the American Trauma Society–Pennsylvania Chapter Award for Injury Prevention, the Allegheny County Safe Kids Physician of the Year Award and The Hospital Council of Western Pennsylvania Award, again, for his injury prevention initiatives. In January 2001, he was awarded an American Academy of Pediatrics' "CATCH" grant to evaluate and improve community resources for children with special needs. Over the past decade, Dr Masiello has had the opportunity to present his injury prevention and public health activities at the Annual Meeting(s) of the AAP and at other state, national and international forums. The countywide bullying prevention program initiated by the CAHWC was depicted on 20/20 ABC TV in 2001 as a model violence prevention program. In May of 2005, Dr. Masiello received the President's Volunteer Service Award by the President's Council on Service and Civic Participation. In July of 2005 he was named as one of the TOP Physicians in Western Pennsylvania Hospital News. Numerous grants have been awarded to support these community-based programs. *In February of 2006, and based on the HP/DP activities of the Office of Community Health, MMC became the first hospital in the US to be designated as a member of the World Health Organization - Health Promoting Hospital Network*.

International Experience: Dr Masiello has worked in Mexico, Indonesia, and Nicaragua. In February of 2005, he served as a medical volunteer for the U.S. Navy and Project Hope relief mission to Banda Aceh, Indonesia. And in September 2005 he returned to the USNS Comfort to assist in the Hurricane Katrina relief efforts.

Discovery and Validation of Breast Cancer Biomarkers Using Proteomics and ELISA Microarrays

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Abstract

Breast cancer is one of the most prevalent cancers in the United States, resulting in the death of ~50,000 women per year. Current methods for early detection (e.g., mammography and breast exam) rely on physical means to detect a tumor and are unreliable. A more useful and accurate evaluation of breast cancer could potentially be obtained by an analysis of proteins in blood. Since breast cancer is a multifaceted disease, it seems likely that a single protein will be insufficient to detect all forms of this disease. In addition, the normal levels of many cancer markers will be affected by age, reproductive history, menopausal status and other epidemiological factors.

Therefore, it seems likely that it will be necessary to use a profile of markers to accurately detect breast cancer and that the accuracy of this profile will be improved by incorporating these epidemiological factors into the analysis. In order to find new biomarkers of breast cancer, we are undertaking proteomic analyses of breast fluids and blood plasma. Based on results of these and other studies, we will analyze up to 40 proteins in ~1000 plasma samples using ELISA microarray technology developed in our laboratory. This number of samples is sufficient to determine the ability of a biomarker profile to detect the presence of early disease and to evaluate whether incorporation of epidemiological factors can improve the accuracy of this analysis.

Biography
Richard Zangar, Ph.D., is a Senior Research Scientist at the Pacific Northwest National Laboratory in Richland, Washington. His current research focuses on the discovery and validation of biomarkers for human diseases, particularly breast cancer.

This work encompasses applied biomarker discovery and validation studies, as well as fundamental studies directed towards understanding the underlying molecular processes involved in biomarker release from cells. His laboratory is currently developing an ELISA microarray platform for the high-throughput validation of cancer biomarkers. He is currently funded by the Early Detection Research Network of the National Cancer Institute.

Translational Medicine: Defining its Role and Future (CME)

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Abstract
The objectives of this presentation are:
1) To understand the difference between translational medicine and translational research
2) To understand the benefits to the physician and the patient
3) To understand its impact on medical practice and personalized medicine

Biography
Michael N. Liebman, Ph.D. is Executive Director of the Windber Research Institute after serving as Chief Scientific Officer since November, 2003. Prior, he was Director, Computational Biology and Biomedical Informatics at the Abramson Family Cancer Research Institute of the University of Pennsylvania Cancer Center since September, 2000. He previously was Global Head of Computational Genomics at Roche Pharmaceuticals and Director, Bioinformatics and Pharmacogenomics at Wyeth Pharmaceuticals. He was also Director of Genomics for Vysis, Inc and Director of Bioinformatics at the Amoco Technology Company. He has served on the faculty of Mount Sinai School of Medicine in Pharmacology and Physiology/Bipohysics. He serves on 12 international scientific advisory boards consults for 5 pharma/biotech companies and has been on the economic development programs in the Philadelphia Life Sciences Sector and the State of Illinois Biotechnology Commission. He is an Invited Professor at the Shanghai Center for Bioinformatics Technology and is currently Chair of the Healthcare Task Force for the SMART program, and on the Human Health and Medicinal Chemistry Commission of the IUPAC. His research focuses on computational models of disease progression stressing risk detection, disease process modeling and analysis of lifestyle interactions.

Biography
Richard Mural, Ph.D. is the Chief Scientific Officer of the Windber Research Institute (WRI), a private nonprofit research institute specializing in issues of women's health. Prior to joining WRI, Dr. Mural was at Celera Genomics (2000-2005) and was part of the team that sequenced the human genome. He managed a group that was responsible for generating the genome annotation that supported Celera and Applied Biosystems customers. He also led Celera's effort to analyze mouse chromosome 16, the sequence of which was generated as part of the whole genome sequencing of the mouse genome performed at Celera. Before joining Celera Dr. Mural was at the Oak Ridge National Laboratory where he was involved with the human genome project since the early 1990s and was actively involved in developing gene-finding algorithms. Dr. Mural received his Ph. D. from the University of Georgia.

Physiological, Psychometric, and Molecular Responses to a Coronary Heart Disease Reversal Program

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Abstract
Objective: Lifestyle and behavioral factors have significant effects on development and progression of coronary artery disease (CAD), but the impact of lifestyle change on molecular risk factors in persons with CAD is not well defined. This study is evaluating changes in physiological, psychosocial, and molecular risk factors during an intensive lifestyle modification program.
Methods: One hundred seventy six individuals have participated in a prospective, nonrandomized, intervention designed to stabilize or reverse progression of CAD through dietary changes, exercise, stress management, and group support. Three examinations over the course of one year assess psychosocial functioning, physiological and molecular CAD risk factors, and risk for future coronary events.
Results: Most participants in this program derive clear benefit in terms of significant reductions in traditional CAD risk factors and improvements in mental health and quality of life.

The program is effective in producing clinically relevant changes in participants suffering from depression, stress, or emotional distress, with response rates better than those observed with traditional pharmacologic interventions. Potentially important molecular changes, as well as functional changes in the cardiovascular system, also have been observed in program participants.

Conclusions: Comprehensive lifestyle interventions have the power to reduce multiple psychometric and physiological risk factors for CAD and produce clinically meaningful improvement in measures of depression, stress, and mental health. Cardiac prevention programs that incorporate lifestyle changes to address both psychosocial and physiological risk factors may be an effective component of comprehensive care for persons with CAD and may produce important molecular changes that drive health improvement.

Biography
Darrell L. Ellsworth, PhD is the Senior Director of the Integrative Cardiac and Metabolic Health Program at the Windber Research Institute. Dr. Ellsworth received his PhD from Texas A&M University in human genetics, served as a Research Assistant Professor in the Institute for Molecular Medicine at the University of Texas, and was a Research Geneticist at the National Heart, Lung, and Blood Institute, National Institutes of Health. He has been actively involved in the design, execution, and management of large multi-center collaborative research projects focusing on genetic influences on complex diseases such as heart disease, obesity, and breast cancer at Windber Research Institute. Dr. Ellsworth has published more than 50 articles, book chapters, and abstracts in peer reviewed publications such as the Lancet Oncology, Nature Genetics, Circulation, Annals of Surgical Oncology, Obesity Research, and the International Journal of Obesity.

The Role of Informatics in Patient Care: A Framework for Personalized Medicine

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Abstract
Evidence-based and personalized medicine are two of the most widely discussed topics in healthcare today. While there is wide agreement on the benefits these practices can have in terms in improved care and reduced cost, there is still limited consensus on how to implement these concepts. The systems requirements are unclear, the regulatory environment is ambiguous, and protocols often do not translate well across clinical centers. In order to develop a truly broad personalized medicine system, clinicians, administrators, and policymakers must begin to address these challenges. Mr. Eberhardt will share some of his observations and experiences with these challenges gleaned from his work with diagnostic modeling. The discussion will present a broad survey of information systems requirements, data requirements, possible implementation architectures, and regulatory concerns, along with example of how such a system could be implemented in cervical cancer and kidney disease.

Biography
Mr. Eberhardt has a Bachelors in Economics and History from Duke, having graduated Cum Laude. Mr. Eberhardt has spent his career in performing complex analysis. Starting as an analyst in Morgan Stanley's investment banking program, he proceeded into a career in Morgan Stanley's venture capital fund, focusing on the analysis and selection of investments in technology. Mr. Eberhardt left Morgan Stanley four years ago to become one of the founders of DecisionQ Corporation. Mr. Eberhardt has spoken previously at conferences on data mining, healthcare, and entrepreneurship, and has published papers on the use of data mining tools for improving patient outcomes in healthcare. Publications include *Application of multivariate probabilistic (Bayesian) networks to the interpretation of diagnostic assays* published in the proceedings of the 2005 AACC Oak Ridge conference in Baltimore, *Classification of pathology data using a probabilistic (Bayesian) model* published in the proceedings of the 2005 International Conference on Systems Engineering,

The p53 Gene in a Controversial Breast Cancer Population –Analysis of Mutations via Bayesian Network Algorithms published in the proceedings of 2005 San Antonio Breast Cancer Symposium in San Antonio, TX, and *Interpreting diagnostic assays by means of statistical modeling* published in the April 2006 issue of IVD Technology.

Less is More: Breast Surgical Diagnosis and Treatment (CME)

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Abstract
The objective of this presentation is:
1) Identify newer methods of breast lesion diagnosis and surgical treatment.

Biography

Dr. Dianna Craig is a board certified general surgeon who specializes in diseases of the breast. Her office is located at the Joyce Murtha Breast Care Center of the Windber Medical Center. She is a member of the American College of Surgeons, American Society of Breast Surgeons, Pennsylvania Breast Cancer Coalition, National Consortium of Breast Centers, American Medical Association, Pennsylvania Medical Society, and the Cambria County Medical Society. She serves as the local Principal Investigator on several clinical trials associated with Walter Reed Army Medical Center involving breast cancer, high risk patients, and breast cancer vaccine protocols. She serves on several committees at Windber Medical Center and actively participates in continuing medical education.

After graduating from high school, she attended the University of Texas in Austin and graduated in 1975 with a Bachelor of Fine Arts Degree in Art and Art Education. She taught art for a short time, and then began a new career in the aerospace defense industry, first as a trainee and then working up to the level of an electrical design draftsman and technical illustrator. After working in this field for fourteen years, she decided to once again change careers when she returned to school part time and obtained her pre-med required coursework followed by passing her medical school entrance exam. She then moved to San Antonio and graduated four years later from the University of Texas Health Science Center with her medical degree. She chose to pursue the field of surgery and completed her general surgical residency here in Johnstown at Conemaugh Memorial Medical Center. During her residency, she spent some time at MD Anderson Hospital on the breast surgery service. After her training in Johnstown, she moved to northern Maine for a few years and was involved in all aspects of general surgery. In the past few years, she moved back to Johnstown and has dedicated her career solely to Breast Cancer and diseases of the breast.

Integrated Analysis in Pathway Discovery: Linking Neuro Biology with Medicine Through Visualization

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Abstract
Objectives: The role and activities of a Health Promoting Hospital will be defined. We will also define the issue of obesity as it relates to Translational Medicine with a final comment on the potential benefit of translational medicine in a community setting.

Methods: A brief history of the development of a Health Promoting Hospital in a U.S. health care system will be offered with an emphasis on the monitoring and evaluation of community based health promotion/disease prevention programs. The speaker will then present a short review of the literature demonstrating the benefit of a co-existence between translational medicine and obesity related public health initiatives in a community setting. A review of the obesity and fitness HP/DP programs implemented, coordinated, monitored and evaluated by a regional health care system will also be presented.

Discussion: The discussion will hopefully entail lively debate regarding the role of a community hospital as a health promoting hospital and the possibilities of incorporating translational medicine as a health promoting partner in addressing the obesity epidemic.

Biography
Dr. Peter van der Spek is Professor and Head of the Bioinformatics Department at Erasmus Medical Center. Prof. Dr. van der Spek's department supports projects that generate genomics and proteomics data from basic research, forensics studies, molecular diagnostics and clinical trials. Peter's own research program combines genomics, proteomics and cytogenetic data to identify genes associated with neurological disorders. Prior to joining Erasmus MC, Peter led the Bioinformatics group at Johnson and Johnson in Beerse, Belgium. He has held a number of other positions in the pharmaceutical industry.

Progress in Breast Cancer and Translational Medicine: The Clinical Perspective

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Abstract
"Translational Medicine" is all the rage in the present healthcare climate. While many people and organizations speak of being involved in "translational" medicine, many if not most do not meet the rigorous criteria that need to be met in order to properly represent true translational medicine and research. The CBCP is one organization that for over five years, has represented the epitome of the translational clinical-basic science research paradigm in the study and treatment of breast cancer and related diseases. In this talk you will learn what it truly means to be working in all areas of what it takes for an organization to be truly "translational," the challenges one faces in doing so, and the promises of such a capability.

Biography
Colonel Craig D. Shriver was born and raised in Reading, PA. He earned a Bachelor of Science (B.S.) degree in biochemistry *cum laude* from Albright College in Reading, PA. He earned his M.D. degree from Temple University in Philadelphia, PA, after winning a Health Professions Scholarship Program (HPSP) scholarship from the US Army. He went on to complete his general surgery residency training at Walter Reed Army Medical Center, and was selected for advanced fellowship training in surgical oncology at the prestigious Memorial Sloan-Kettering Cancer Center in New York. He has published over 80 academic papers in the medical literature, including as one of the Lead Authors on the seminal article on sentinel lymph node biopsy in breast cancer, published in October 1998 in the world's most prestigious medical journal, the New England Journal of Medicine, and again was a Lead Author in the New England Journal of Medicine in December 2004, in a work describing the care of the casualties from Operation Iraqi Freedom returning to Walter Reed.

COL Shriver became Program Director of the Walter Reed Army Medical Center General Surgery residency in June 1998, became Director of the Clinical Breast Care Project (CBCP) in February 2000, and became Chief of General Surgery at Walter Reed in April 2001, all positions which he presently holds. As Director and Principal Investigator of the CBCP, along with Nick Jacobs, FACHE of the Windber Medical Center, they are the co-founders of the Windber Research Institute made possible through the support of The Honorable John P. Murtha.

Identification of Blood-Based Biomarkers to Detect Breast Cancer

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Abstract
Array-based gene expression profiling has become a common tool to study the molecular basis of complex diseases. In many cases, the availability of primary tissue is limited; consequently, blood is commonly used for clinical research due to its easy accessibility. However, expression profiling of blood can be challenging due to the varied population of cells and the large proportion of globin mRNA found in whole blood. Approximately 70% of mRNA transcripts in blood are comprised of globin; this large abundance of globin transcripts has been shown to decrease detection sensitivity and increase sample variability on Affymetrix expression arrays. Using the GLOBINclear-Human kit (Ambion) to deplete total blood RNA samples of globin mRNA, we have found that the percentage of transcripts called present on microarrays increases an average of 12%, resulting in over 2000 more low-abundance transcripts being detected. Using this technology, we will generate gene expression profiles from 20 node-negative patients with breast cancer, 20 node-positive patients with breast cancer and 20 controls to determine if biomarkers exist in peripheral blood that can (1) distinguish between patients with and without breast cancer and (2) discriminate between positive or negative lymph node status. These results will determine if gene expression profiling of whole blood is a worthwhile approach to studying breast cancer and if so, may lead to blood-based diagnostic tools for this disease.

Biography
Lori Field, Ph.D. is a post doctoral fellow in the Molecular Genetics of Breast Disease research group at Windber Research Institute. Lori received her B.S. in biology from Elizabethtown College and her Ph.D. in Environmental Health Sciences from Johns Hopkins University Bloomberg School of Public Health. Her primary research focus is to identify molecular factors that cause African American women to develop more aggressive and deadlier forms of breast cancer than Caucasian women.

AskAFIP™ Knowledge Portal Provides World-Wide Access to Vital Medical Resources

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Abstract
In today's increasingly complex world of medical science, one of the more valuable and comprehensive sources of archival medical information available to medical professionals are the vast collections of the Armed Forces Institute of Pathology (AFIP). Recognizing the unique value of their ever-expanding collections, AFIP and Information Manufacturing Corporation (IMC) jointly developed AskAFIP™, a sophisticated knowledge portal accessible almost anyplace, anytime through the Internet.

Built using the latest Internet technologies, AskAFIP™ is a custom designed decision support and distance learning portal, which allows world-wide access to the entire AFIP digital archives. Users can review unique pathology cases, browse the Institute's virtual bookshelf and medical journals, or link to other parts of the portal from their PC using a standard web browser. Distance learning is facilitated and Continuing Medical Education (CME) credits can be earned while using AskAFIP™, fulfilling the ongoing need for required professional medical education.

AskAFIP™ users benefit from access to a wide variety of materials in the AFIP collections; including cases from the case repository with very high-quality digitized histopathology slides, information from the AFIP/ARP (American Registry of Pathology) Atlases of Tumor and Non-Tumor Pathology, and the Radiologic Pathology Course Syllabus. Articles published by AFIP staff, audio and video sessions of recorded medical education classes, seminars, and conferences, and important information on the most current and pressing medical issues like SARS and AIDS are also available. AskAFIP™ (www.AskAFIP.org) is a free service to military professionals and available on a subscription basis to all others.

Biography
Mr. Bruce Lister is Senior Program Manager for Information Manufacturing Corporation. He is currently responsible for development and operations of the AskAFIP™ portal at the Armed Forces Institute of Pathology. Mr. Lister has extensive technical design, operations and program management experience and has been a principal technical contributor and manager for numerous programs at leading companies like GTE, GEICO Insurance, Network Solutions, VeriSign, Dassault, Hughes and SIAC.

Mr. Lister's technical and managerial accomplishments include the development and implementation of a major distributed billing system for GTE, Chief Architect and Project Manager for GEICO Insurance's rapid insurance quote system, Chief Architect and Project Manager for the design and implementation of Oracle ERP systems at Network Solutions and VeriSign, manager of a major Oracle-based Data Warehouse with input feeds from 14 disparate systems, and development of custom reporting systems; including an Executive Management Dashboard. Mr. Lister managed worldwide corporate intranet services for VeriSign.

His contributions at Hughes include the development of satellite imagery analysis and processing systems. At Dassault, he developed a unique 3D algorithmic paradigm called NURBS that was used as the internal engine for their 3D CAD/CAM product line; resulting in three patents. While with SAIC, Mr. Lister developed an optical character recognition (OCR) system that became the core of their commercial document conversion system and proved to be one of the most accurate in the world.

Mr. Lister's earlier experience included conducting medical research protocols for Nobel Laureate Torsten Wiesel at the Neurobiology Department at Harvard Medical School. He also prepared histology slides of brain tissue used in vision processing research. He researched and developed a computer aided system for analysis of real-time visual cortex cellular responses, and developed a 3D map of their cellular activity and interactions within the visual cortex.

Mr. Lister holds a B.A. in Biomechanical Engineering with additional studies in neurobiology and computer sciences from Harvard University. He also holds a Certificate in Artificial Intelligence from the University of Southern California.

MicroRNA Expression Profiles: Novel Tools for Cancer Classification?

Giuseppe Russo, Ph.D.
Post Doctoral Fellow
Sbarro Institute
Temple University

Abstract

Objectives: The importance of cancer classification will be defined. The speaker will uncover mechanisms, properties, possible uses and potential benefits of microRNAs as novel biomarkers in cancer research.

Methods: A comprehensive overview of microRNAs will be shown with particular emphasis on the latest information available. The speaker will then present a critical analysis of current studies related to microRNA expression profiles in cancer research.

Discussion: The discussion will focus on the role of microRNAs as cancer genes and the interesting prospective of incorporating microRNAs as novel biomarkers in cancer research.

Biography

Dr. Russo received his B.S. and M.S. degrees in Biological Sciences (*magna cum laude)* in 1997 from University Federico II of Naples, Italy and his PhD in Diagnostic Quantitative and Molecular Pathology (*special mention of honor*) in 2005 from University of Siena, Italy. Dr. Russo has more than 34 international papers in abstracts and scientific journals in the field of Cancer Research. Dr Russo was awarded by European School of Medical Genetics, and he recently obtained two high military honors in Italy. Dr. Russo is member of American Association for Cancer Research (A.A.C.R.), American Association for the Advancement of Science (A.A.A.S.), International Society for NeuroVirology (I.S.N.V.), Young European Biotech Network (Y.E.B.N.) Italian Association of PhDs (A.D.I.) and Bioinformatics.org. Dr. Russo officially reviews world-wide studies submitted to *Journal of Cellular Physiology* and *International Journal of Cancer*, as well as Biotech technologies and related software. Dr. Russo's research combines Molecular and Cell Biology approaches with innovative biotechnologies and bioinformatics tools relevant for the identification of biomolecular markers involved in Cancer Research. Dr. Russo is currently appointed as Leader Research Scientist and Project Manager at Sbarro Institute for Cancer Research and Molecular Medicine, Temple University, Philadelphia, Pennsylvania.

POSTERS

Maestra Software in Genome-Wide and Candidate Gene Analysis: A Case Study

Steven Ringquist, Ph.D.
Director of the Molecular Genetics of Breast Cancer
Windber Research Institute

Christopher Pecoraro, Ying Lu, Lorenzo Pasquali, Alexis Styche, William A Rudert, Massimo Trucco and Steven Ringquist
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Data intensive laboratory projects require the use of technology to manage information and knowledge. A successful study into the genetics of complex disease has many components: 1) initial setup of genotyping assays; 2) data viewing; 3) statistical analysis of results; and 4) skillful presentation of information. Challenges exist when attempting to present new knowledge resulting from statistical genetic analysis. Data management from a high throughput screen can be aided through the use of computer technology. MAESTRA: "Management Application for Extensive SNP Typing Reporting and Analysis" software facilitates this process. MAESTRA represents a complete laboratory information management system. The software provides a simple, real-time, remote, and macro-level view of the genotyping laboratory. High throughput screening data from microarray analysis (Genome-Wide Screen) and from SNP genotyping (Candidate Gene Screen) have been used to evaluate the software. The case study resulted in genetic association of human disease with various chromosomal regions, displayed in the form of a genome-wide "hot-spot" map where the linkage score for each candidate is illustrated as a color-coded location on a chromosomal map. The software enabled comparison of the results with chromosomal position, genetic region, and haplotype data composed from the dbSNP, Entrez Gene, and HapMap databases stored in the MAESTRA data warehouse. An integral component of a genotyping study into the genetics of diabetic nephropathy, MAESTRA continues to be developed in the laboratory as part of ongoing research into the genetics of a complex disease.

Online Analysis of Highly Dimensional Biomedical Data to Support Personalized Medicine

Mick Correll
Manager of Professional Services
InforSense

Mick Correll[1], Michelle Osmond[1], Jim Clark[1], Leonid Kvecher[2], Richard Mural[2], Craig D. Shriver[3], Hai Hu[2], and Michael N. Liebman[2]

[1]Inforsense LTD. [2]Windber Research Institute. [3]Walter Reed Army Medical Center.

Researchers at the Windber Research Institute are working with informatics platform-vendor InforSense to realize a ground-breaking approach to women's health and breast cancer treatment in particular. The goal is to clarify the link from genetic make-up to disease expression, and so enable clinicians to make improved choices when treating patients. The collaboration between InforSense and Windber has resulted in the development of an informatics platform for Translational Medicine able to support the needs of researchers and clinicians alike. This Poster describes the portal interface which has been developed to enable both clinicians and informatics researchers to navigate highly dimensional biomedical data in an intuitive web interface

Genomic Alterations in Primary Breast Carcinomas Do Not Predict Axillary Lymph Node Metastasis

Rachel Ellsworth, Ph.D.
Director of Women's Health Research
Windber Research Institute

Rachel E. Ellsworth, PhD, Darrell L. Ellsworth, PhD Brad Love, PhD, Jeffrey A. Hooke, MD, Craig D. Shriver, MD

Background: Axillary lymph node status is one of the most important prognostic factors in treatment selection for patients with breast cancer. Several genetic studies attempting to identify molecular profiles have produced conflicting results, thus it is unclear whether genetic changes in the primary breast tumor are predictive of lymph node involvement. This study examined allelic imbalance (AI) in primary breast tumors from node-negative and node-positive patients to determine whether patterns of genomic changes can be used to identify metastatic breast cancers.
Methods: Laser microdissected DNA samples were collected from primary breast tumors of 50 patients with positive lymph nodes and 50 patients with negative lymph nodes. Fifty-two microsatellite markers representing 26 chromosomal regions commonly deleted in breast cancer were used to assess patterns of AI.
Results: Overall AI frequencies between node negative (25%) and node positive (26%) breast tumors did not differ significantly (P=0.3888). When the data were examined by chromosomal region, only chromosome 9p21 showed a higher frequency of AI events in the node negative samples (29%) compared to the node positive samples (9%), although this difference did not reach statistical significance (P=0.0625).
Conclusions: Axillary lymph node metastasis may be considered a marker of advanced carcinomas, but the inability of genome-wide AI events to differentiate node negative from node positive breast tumors suggests that nodal metastasis is largely independent of genomic alterations in the primary tumor. As recent molecular studies suggest that lymph node metastasis occurs early in tumor development, molecular profiling of primary breast tumors may have limited prognostic value in predicting lymph node status.

Identification of cSNPs in Environmental Response Genes Contributing to Breast Cancer Etiology

Rachel Ellsworth, Ph.D.
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Sporadic cancer is likely caused by a number of DNA variants, each making a small contribution to overall cancer risk. The Environmental Genome Project has identified 65 potentially deleterious cSNPs in 47 genes involved in metabolism of toxins, drug clearance, and DNA repair with population frequencies ranging from 0.01 – 0.38. To determine whether these cSNPs contribute to breast cancer etiology, we examined the prevalence of these variants in women with invasive breast cancer (n=150) and age- and ethnicity-matched (n=150) female controls enrolled in the Clinical Breast Care Project (CBCP). The patient population was comprised of ~1/3 African American and 2/3 Caucasian women; other minority populations were excluded due to small sample size. Associations between DNA variations and numerous environmental exposures (reproductive and lifestyle choices, diet, geography, and health history) were examined. Genotypes were determined by RFLP assays or by direct sequencing. Allele frequencies were not significantly different from published values for many of the cSNPs; most showed low minor allele frequencies ($\leq$0.01), although rs17655 (ERCC5), rs1801133 (MTHFR) and rs1801131 (MTHFR) had relatively high minor allele frequencies (>0.20). Allele frequencies differed significantly (P<0.05) between women with breast cancer (cases) and healthy controls for SNPs rs1799950 (BRCA1), rs1799853 (CYP2C9), rs4252633 (ERBB2), rs1800124 (ERCC4), and rs4648099 (NFKB1).

Although rs1799950, representing the Q356R variant of BRCA1, was classified as a polymorphism in the Breast Cancer Information Core database and generally not considered causative in patients with hereditary breast cancer, the high frequency of this variant in women with invasive breast cancer (13%) versus controls (1%) suggests that Q356R may play a functional role in breast cancer pathogenesis. While the frequency of the Q356R variant was not statistically different in Caucasian and African American women with breast cancer, the W452C variant in ERBB2, was found exclusively in African American women ($P<0.01$), none of whom were HER2+, either by IHC or FISH analysis. Functional variants in environmental response genes, may therefore, impair the ability to respond to exogenous exposures and increase the risk of developing breast cancer.

Patterns of Genomic Instability Differentiate Clinical Outcomes in Patients with Invasive Breast Cancer

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Rachel E. Ellsworth, Tyson E. Becker, Darrell L. Ellsworth, Brad Love, Jeffrey A. Hooke, Craig D. Shriver

Background Despite improved survival rates for women with breast cancer, aggressive therapies may result in the over treatment of many with undesirable physical and economic costs. Identification of molecular profiles in breast tumors that differentiate patients with poor prognosis from those with favorable outcomes would allow for development of effective, customized treatment regimens.
Methods DNA was extracted from primary breast tumors representing stage I (n=75), stage II (n=42), stage III (n=24), and stage IV (n=9) after laser microdissection to isolate pure tumor cell populations. Genomic instability was detected using 52 microsatellite markers representing 26 chromosomal regions frequently altered in breast cancer. Statistical analyses were performed using Fisher's exact tests and Student t-tests.
Results Patients with poor prognosis (15%) were defined as those dead of disease (DOD) or alive with disease (AWD), either metastatic disease or disease recurrence; all others had no evidence of disease (NED). Overall levels of genomic instability were significantly higher in tumors from patients with poor prognosis ($P<0.0005$). At the chromosomal level, chromosome 17p13.3 ($P<0.001$), 3p13 ($P<0.05$), and 13q14 ($P<0.05$) were altered significantly more frequently in patients with poor prognosis compared to NED patients.
Conclusions Chromosomes 3p13, 13q14, and 17p13.3 harbor the fragile histadine triad (FHIT), retinoblastoma 1 (RB1), and hypermethylated in cancer 1 (HIC1) genes, respectively. Alteration of the FHIT gene may promote overall genomic instability while alterations in RB1 and HIC1 has been associated with poor prognosis in patients with breast cancer. Assessment of genomic instability at these three regions may prove useful for stratifying patients by tumor aggressiveness, thus allowing more effective, customized treatment options to be developed.

Implementation of the Batch Processing Approach for Two Dimensional Differential In-Gel Electrophoresis on Clinical Breast Cancer Serum

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Breast cancer is one of the leading causes of female mortality in the world, with approximately 41,000 individuals dying annually in the United States alone. There is an urgent need for biomarkers that could be used to detect early-stage breast cancer before the disease reaches a more progressive and less curable state.

Currently, proteomics is one of the technologies being applied to biomarker discovery research, and has shown great promise in discovering proteins that reflect pathological states. Two dimensional differential in-gel electrophoresis (2D-DIGE), a proteomic tool utilized to separate proteins from a complex mixture such as serum, makes possible the direct comparison of protein expression levels between samples. 2D-DIGE can then be coupled with mass spectrometry to identify the differentially expressed proteins. Herein, we describe a 2D-DIGE batch processing approach that was applied to twenty-two clinical samples in an effort to discover potential biomarkers. The advantage of batch processing over pair-wise analysis is that it minimizes gel to gel and sample to sample variations. Furthermore, this high throughput method uses less sample and reagents as well as reduces analysis time by mass spectrometry significantly. In this study, sera from eleven individuals diagnosed with breast cancer and sera from eleven healthy individuals were subjected to 2D-DIGE. Through employment of the DeCyder (GE Healthcare) Software's Biological Variance Analysis (BVA) module, forty-six differentially expressed proteins were found with 95% confidence, and the majority of them were subsequently identified using mass spectrometric analysis. A few of the proteins identified in this study are already under investigation as potential biomarkers due to their implications with cancer.

Proteomic Analysis of Low Abundance/Low Molecular Weight Proteins from Blood Serum for the Biomarker Discovery of Breast Cancer Disease.

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Biomarker discovery research using various proteomic technologies in blood serum/plasma, is gaining prominence recently as this may provide a minimal invasive method for detection of various diseased states such as breast cancer. Serum or plasma is a complex mixture of proteins having dynamic ranges of protein concentration that vary up to 10^{12} orders of magnitude with concentration ranges from <<pg/ml to >>mg/ml.

The most high abundance proteins constitute >90% of the total serum proteome, and therefore interfere with the detection of low abundance/low molecular weight proteins using standard detection technologies such as 2D-DIGE/MS. The low abundance/low molecular weight proteins are the proteins from tissue leakage, cytokines and peptide hormones etc. In a diseased state, such as breast cancer, some specific proteins/peptides are released in higher amounts than under normal condition. Identification and quantification of these low molecular weight proteins/peptides (potential biomarker) in serum from breast cancer patients could thus give us a method for the early detection of breast cancer.
To enrich low abundance/low molecular weight proteins from serum we have taken two different approaches. The first method involves organic solvent precipitation method to remove majority of the high abundance/high molecular weight proteins. The low molecular weight proteins in depleted serum could subsequently be concentrated and analyzed by 2D-DIGE/MS and MALDI-MS. Our initial analysis of a small set of serum samples from breast cancer patients and normal individuals indicated the presence of differentially expressed proteins (2D-DIGE) and peptides (MALDI-MS) in breast cancer samples. We are continuing our analysis with a larger set of samples to validate our results and to identify the differentially expressed proteins/peptides that could serve as potential biomarkers for breast cancer disease.

The second method involves ultrafiltration of serum using 50 kDa cut-off filters to enrich proteins of molecular mass <50 kDa. Following ultrafiltration we have analyzed protein samples by LC-MS/MS (MudPIT) experiment that yielded about 150 high confidence proteins. We will eventually perform LC/MS experiments on depleted serum samples from breast cancer patients and the data will be analyzed by DeCyderMS software to identify differentially expressed proteins/peptides (potential biomarkers). The result of this analysis will also be presented.

Breast Pathology Co-Occurrence in Stratified Populations Implications for Breast Cancer Development in Different Patient Populations

Susan Maskery, Ph.D.
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Windber Research Institute

Susan Maskery, Yonghong Zhang, Hai Hu, Jeffrey Hooke, Craig Shriver, Michael Liebman

OBJECTIVE: Previously we showed significant variation in the clinical presentation of breast disease and cancer between pre and post-menopausal women. We have expanded this study to analyze breast disease pathology in patients stratified by BMI, parity, and race. Our study population is from the Clinical Breast Care Project (CBCP) between Windber Research Institute and Walter Reed Army Medical Center.
DESIGN: Each case is reviewed and annotated by a single pathologist who records the occurrence of any and all of 131 possible breast pathology and lymphoid diagnoses that co-occur within each patient's specimen(s). Co-occurrence between two diagnoses is assessed by the Jaccard coefficient, and is separately assessed in the following eight sub-groups: BMI>25 vs. BMI<25, parous vs. non-parous, African American vs. Caucasian, and pre vs. post-menopause.
RESULTS: Similar to other studies, we observe African American women and pre-menopausal women are more likely to be diagnosed with high grade cancer compared to Caucasian and post-menopausal women respectively. Significant variation in breast pathology is seen in groups stratified by race, BMI, and menopausal status, but not in groups stratified by parity.
CONCLUSION: Co-occurrence analysis of this well characterized, highly annotated, and standardized pathologic set of breast diseases and cancers will lead to identification of complex pathologic associations between patients such that we may begin to identify differences in clinical presentation of breast cancer between different patient populations.

Separate DCIS Progression Pathways Derived from Breast Disease Heterogeneity Data

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Windber Research Institute

Susan Maskery, Hai Hu, Richard Mural, Craig Shriver, Jeffrey Hooke, Michael Liebman

Background: Observation of heterogeneity in breast pathology has been a consistent theme but one that has had little detailed analysis and/or interpretation. Typically, this research has been limited due to variation in pathology description by different pathologists. We have utilized a unique breast disease tissue and data repository to infer multiple pathways from breast disease to breast cancer.
Methods: Breast pathology diagnoses are drawn from 1232 standardized and highly expanded pathology reports. A single pathologist records the occurrence of any and all pathologies seen in a patient's breast biopsy. This co-occurrence data is analyzed using a Bayesian network learning algorithm that links data observations in a probabilistic order of events.

The resultant Bayesian network is a visualization of how breast disease diagnoses can predict the presence or absence of other diagnoses. For example, a connection between ductal carcinoma in situ (DCIS) and invasive ductal carcinoma (IDC) visualizes the statement: the presence of DCIS alters the likelihood of the presence of IDC.
Results: Separate pathways are implicated for DCIS grade 1 (G1), DCIS grade 2, (G2) and DCIS grade 3 (G3). These pathways are: postmenopausal-DCIS G1-IDC G1; ADH-DCIS G2-IDCG2; DCISG3-IDC G3. That different DCIS grades have very different co-occurrence patterns implies these three pathologies may be 3 separate diseases.

Conclusions: Bayesian network analysis provides a mechanism for the use of heterogeneity in breast disease pathology to predict multiple breast disease pathways. Using novel bioinformatic techniques we provide evidence that DCIS progression follows three separate pathways. Parallel genomic studies at our institute imply DCISG1, DCISG2, and DCISG3 are separate genomic entities.
breast cancer between different patient populations.

Variation in breast disease co-occurrence frequencies between pre- and post-menopausal women

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Susan Maskery, Yonghong Zhang, Hai Hu, Craig Shriver, Jeffrey Hooke, Michael Liebman

It is known that 1) breast cancer presents as a heterogeneous mix of pathologies whose origins are poorly understood and 2) menopausal status significantly influences a woman's risk for developing breast cancer. We hypothesize that patterns in breast pathology co-occurrence may be different in pre- vs. post-menopausal women, and further, that identification of variation in pathology co-occurrence between these two populations may yield novel testable hypotheses for breast cancer development. The Clinical Breast Care Project (CBCP) between Windber Research Institute and Walter Reed Army Medical Center has generated a vast knowledge base of breast disease and breast cancer data in the form of a highly annotated tissue and biospecimen repository and a database of life history data for each CBCP patient. We analyzed the co-occurrence of multiple diagnoses within 889 CBCP patient pathology reports. Consistent pathologic quality is maintained by having each case reviewed and annotated by a single pathologist who records the occurrence of any and all of 131 possible breast pathology and lymphoid diagnoses that co-occur within each patient's specimen(s). Six statistically significant variations in dual pathology diagnosis co-occurrence are identified between post-menopausal and pre-menopausal women.

Relationship Between Educational Level And Breast Cancer

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Background: In the Clinical Breast Cancer Project (CBCP), comprehensive demographic and medical data collected from patients consisting of over 450 fields has gone through extensive QA procedures. A specific advantage of the CBCP is that military family members / patients have equal access to healthcare upon diagnosis which rules out many socio-economic factors from data interpretation. Here we present the results of a preliminary study on the demographics in relation to pathological categories and tumor stages.
Methods: Patients undergoing biopsy (n = 933) were placed in four pathological groups: invasive carcinoma (Invasive); lobular or ductal carcinoma in situ (IS); atypical hyperplasia (Atypical); and benign.

Tumor stage was determined according to AJCC standards. Analysis was done using SPSS and age of diagnosis, ethnicity, education level, and tumor stage were included in the analysis.

Results: Patients with higher education (4-year college degrees or higher, n=580) have fewer Invasive cases (26.0%, p=0.015) than those with lower education (no 4-year college degree, n = 241; 34.4%). We also observed a trend that the former population have more IS and Atypical cases than the latter. There is no difference in educational level among White, African, Asian, Hispanic and others ethnic groups (n=595, 208, 52, 55, and 23 respectively; although some education data are missing). Patients with higher-stage breast cancer (II, III or IV; n = 118, mean ± SD = 56.47 ± 14.61, p = 0.01) are younger than those with lower-stage cancer (0 or I; n = 194; 60.53 ± 12.64).

Education	**Pathology (percentage within education group)**				
	Invasive	***IS***	**Atypical**	**Benign**	**Total**
Lower	83 (34.4%)	18 (7.5%)	7 (2.9%)	133 (55.2%)	241 (100.0%)
Higher	151 (26.0%)	62 (10.7%)	33 (5.7%)	334 (57.6%)	580 (100.0%)
Total	234 (28.5%)	80 (9.7%)	40 (4.9%)	467 (56.9%)	821 (100.0%)
*p-value	0.015	0.156	0.091	0.527	-

* Pearson Chi-Square test

Discussion: Our observation that invasive cases are fewer in patients of higher educational levels cannot be attributed to socio-economic factors since our patients' accessibility to healthcare is equal at time of diagnosis and is independent of educational or ethnic backgrounds. One explanation of the data is that people with a higher education are better informed and so are more likely to proactively attend for medical examinations when the disease is less severe so that the Invasive percentage is lowered. It is also possible that the higher education population has a different life style so the prevalence of the Invasive disease is lower. The finding that patients with higher-stage cancer are younger than those with lower-stage is also intriguing. The above relationships mined from the CBCP database show that careful collection, data cleansing and analysis is of significant importance in breast cancer research.

Correlation of Gene Expression Profiles of Breast Cancer Patients With Tumor Detected by Mammographic Screening or Other Methods

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Introduction: Mammography screening is one of the most effective and widely used tools for the early detection of breast cancer. However, less than 30% of breast cancer cases were detected by this method. Joensuu et al published results (JAMA Sep 2004) indicating that patients had an improved 10-year disease-free survival if their cancerous tumors were first detected by mammographic screening as opposed to clinical- or breast-self exam. We compared gene expression profiles of patients with mammographically versus non-mammographically detected breast cancers, in an attempt to identify potential molecular markers that might be associated with the Joensuu findings.

Material and Methods: We identified 49 patients with tumors from our CBCP microarray database that fit the criteria (unilateral invasive breast carcinoma, greater than 1 cm in size and node-negative) used by Joensuu et al. Blood RNA from these 49 patients were isolated and used for microarray analysis using CodeLink UniSet Human 20K Bioarrays. Among these patients, 22 had tumors that were detectable by mammography screening (MMG) while 27 were not detectable by this method (NONMMG). The raw signal intensities from the microarrays were imported into GeneSpring data analysis software (Agilent Technologies) and normalized using global normalization.

Differentially expressed genes were identified based on a fold-change and used for hierarchical clustering. Among these 49 patients, 35 are Caucasian, 7 African Americans, 2 Asian Americans, 4 Hispania, and 1 Native American. We studied only those 35 Caucasian patients to avoid potential bias caused by the different ethnicities.
Results: We identified 11 genes that had greater than 1.7 fold differences in expression between MMG and NONMMG samples. Using these 11 genes, we were not able to separate all 49 samples into two cluster groups. However, when we studied only those 35 Caucasian patients, we were able to identify 8 genes and used them to separate these 35 samples into two groups. One cluster was composed of 15 MMG samples and 4 NONMMG samples while the other group contained 5 MMG samples and 11 NONMMG samples. Further stratification on the basis of Lymph Node positive and Lymph Node negative did not provide any improvement in clustering because of small sample size.
Discussion: Microarray results relating to expression of 19982 genes in white blood cells from cancer patients could not identify genes that were suitable for clustering analysis on the original samples. After using a subset that contained only Caucasian samples, we were able to identify genes that could be used in hierarchical clustering with a degree of sensitivity at 75% and specificity at 73%. We further stratified these samples based on Lymph Node status. Used only Lymph Node positive samples, we were able to identify genes that can be used in hierarchical clustering. But due to the small sample size, degree of sensitivity and specificity might not be meaningful. These results indicated that with proper experiment design and classification of samples, molecular markers can be identified using microarray technology and the potential use of microarray technology as diagnosis tool.

Molecular Profiling of Human Breast Cancer with Serum Mass Spectrum Data

Yonghong Zhang, Ph.D.
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Sera from 120 Clinical Breast Care Project (CBCP) participants in 6 pathological categories, invasive carcinoma, carcinoma *in situ*, atypical hyperplasia, neoplastic benign disease, non-neoplastic benign disease, and normal breast were analyzed using liquid chromatography and mass spectrometry (LC-MS). Multiple artificial neural network models were built with the serum LC-MS data. These multi-class classification models predicted independent pathology categories with an overall accuracy of 77.8%, and a very high accuracy in predicting invasive breast carcinoma (94.8%). Our results suggest that the serum protein profile can be potentially used to aid clinical diagnosis and treatment of human breast diseases, including cancer.

Developing a Predictive Model for Breast Cancer Risk,

Windber High School
Windber, PA

Heather Bahorik, Toni Boyer, Laura Deyarmin, Kaylee Hollern, Steve Hudak, Nate Pallo, Jason Ward, Mr. Robert Culp, Advisor

A study was undertaken as an extension of last year's population based analysis of the occurrence of breast cancer and obesity in Cambria and Somerset counties and how they related to Lackawanna County, the state of Pennsylvania and the United States overall.

This year's study focused on the patient data collected in the Clinical Breast Care Project that involves Walter Reed Army Medical Center and Windber Research Institute. We examined the parameters that have been established to show a relationship to breast cancer incidence in the CBCP population.

In addition, we added several unique parameters including history of breast feeding, use of birth control, level of education and individual patient breast pathology.

We will report on our approach to constructing a model to predict breast cancer risk based on the old and new parameters and will describe the approach to model building and our experiences and results.

Varied Percentages of Sequential Blood Extraction and the Consequential Effects on Common Blood Values

Bedford Area School District and Everett Area School District

Bartholow, A.; Cessna, A.; Gelvin, N.; Kline, J.; McMillen, J.; Patel, K.; Rowley, S.; Will, A.; Williams, C.

The Blood Volume Withdrawal in Donor Goats study performed will provide data to demonstrate that the blood volumes withdrawn from donor goats at the Lampire Biological Laboratories, Inc., animal facilities do not adversely affect the condition of the animals such that they are unable to thrive in a managed agricultural environment. This study will be performed at the Lampire Biological Labs, Inc., Everett, PA facility by trained Lampire personnel in conjunction with students from the Everett and Bedford school districts. The animals selected to participate in the study will be evaluated as to their overall health, age, hematocrit, current bleeding frequency, anticipated future schedule of bleeding, vaccination and deworming schedule, hoof trimming schedule and any other factors as determined by the Everett Animal Facility Manager to potentially impact the study.

New Product Development: A Novel Cell Culture Device

Greater Johnstown Career and Technology Center

Ahlborn K,; LaFountain, T.; Lester, T.; Moschgat, G.; Reynolds, S.

The project will focus on the culture of cells in Lampire's new Tissue Culture Bag. The new TC Bag that has been developed by Lampire offers greater gas permeability and has been shown to increase the number of cells able to be grown without the need for additional equipment or materials. The students will focus on performing cell culture in the Lampire TC Bag as well as a competitors bag to generate comparative data to present to Lampire. The study will focus on the evaluation of the data and to determine if the Lampire Bag outperforms the competitor's bag in the areas of cell growth, rate of death and viability of the cells over time. The students will also make recommendations as to potential improvements based upon the usage of the Lampire TC Bag as well as the competitor's bag in order to potentially be implemented into the next generation of product development.

Adventure into the Biotechnology Market

Ferndale Area High School

Richard Henry, Jessica Jung, Kayla Smith, Sara Smith, Kristina Stroscio, Kylee Taylor

The student team will assist with the implementation of the first stage of creating a business-marketing plan for ITSI Biosciences. The first stage in the development of the comprehensive Marketing Plan for ITSI Biosciences will involve defining the objectives and determining the target audience.

This aspect has largely been completed. The next stage is the administration of questionnaires to the identified audience. The purpose of the questionnaire is to gain information and knowledge of the current proteomic, bioanalytical and laboratory reagent needs of research scientists in both academia and industry. The students should be assured that the ignorance of this segment of biology is acceptable.

REPORTABLE OUTCOMES

The Army's Telemedicine & Advanced Technology Research Center and the Navy's Naval Health Research Center have both recommended follow-up proposals to form a Working group and/or perform a Mission Area Analysis to identify DOD resources for advanced studies in genomics, proteomics, and biomedical informatics.

" (U) On 14 August 2006, the Telemedicine and Advanced Technology Research Center (TATRC) organized a sidebar workshop as part of the annual Windber Research Institute (WRI) biotechnology conference. WRI executes a number of TATRC managed programs in tissue micro-array analysis, genomics, proteomics and broadband advanced networking/data storage. The workshop in Johnstown, Pennsylvania was attended by about 25 academic, industry and government WRI/TATRC partners. The key workshop speaker was Dr. Leroy Hood, MD, Phd, Director, Institute of Systems Biology in Seattle, Washington. Dr Hood has published over 600 papers in molecular biotechnology and genomics, is inventor of automated DNA sequencing, and has co-founded over 10 biotechnology companies, including the world's largest, AMGEN. Dr. Hood shared his insights on life science translation best practices. He also noted that he felt the Military Health System (MHS) was in a unique position to advance biomedical informatics because of its excellent infrastructure of Electronic Health Records, Clinical Data Repositories and Tissue Analysis programs. BG (Ret) Dr. Michael Dunn, MD, Chief Medical Officer, WRI agreed with this assessment, and suggested that a military Mission Area Analysis of MHS longitudinal clinical informatics and emerging databases of tissue micro-array analysis, genomics and proteomics be considered. The group agreed with this recommendation. Dr. Hood agreed to participate in such a study, if initiated.(U)"

Conrad Clyburn, Special Assistant, MCMR-ZB-T/34052/clyburn@tatrc.org"

DRAFT POINT PAPER *August 23, 2006*
POC: Dr. Frank Garland
Naval Health Research Center
San Diego, CA

"Subj: PROPOSAL FOR DEVELOPMENT OF A WORKING GROUP TO IDENTIFY DOD RESOURCES FOR ADVANCED STUDIES OF GENOMICS AND PROTEOMICS

BACKGROUND

Recently there have been major engineering and technical advances in the fields of genomics and proteomics that support an integrated biological systems approach to disease treatment and prevention. The DoD has access to unique biological repositories consisting of stored tissues and blood combined with detailed demographic and medical databases that provide a critical resource for a concerted translational medicine effort that could leverage this new systems biology approach to improve treatment and elucidate mechanisms of disease prevention. There are now a number of Special Congressional Interest Projects focused on cancer, diabetes, and other health issues that could be coordinated to move these systematic treatment and disease prevention efforts forward.

A TATRC sponsored meeting was held at the Windber Research Institute under the leadership of Mr. Conrad A. Clyburn to identify possible collaborations and establish a working group to coordinate and guide these research efforts. The group that met included representatives from TATRC, the Windber Institute, the Naval Health Research Center, the Institute for Systems Biology, the United States Military Cancer Institute, the Homestead Clinical Corporation, the Walter Reed Army Medical Center Clinical Breast Care Project, and the National Functional Genomics Center. It was proposed that a Working Group be established under the auspices of TATRC, to review and identify DoD resources and develop a coordinated systems research program.

DISCUSSION

Department of Defense service members and their families comprise one of the largest defined populations in the world with uniform access to health care and centralized sources for routinely collected medical and demographic information. These rich data resources are combined with unparalleled tissue and serum repositories that include more than 40 million frozen blood serum samples for over eight million service members going back as far as 1985 at the Army Medical Surveillance Activity. The Armed Forces Institute of Pathology has thousands of tissue samples. Information for other DoD populations such as reservists and dependents also provides fertile ground for investigation. The Walter Reed Army Clinical Breast Care Project and the Windber Research Institute have established tissue repositories that include both service members and dependants, with over 23,000 tissue samples.

RECOMMENDATION

Form an Advanced Studies of Genomics and Proteomics (ASGP) Working Group to develop a coordinated approach to utilizing these unique DoD biological and data resources. Co-chairs would be Mr. Conrad A. Clyburn, Director of Program Integration and Planning, TATRC; and Dr. Frank Garland, Technical Director, Naval Health Research Center. Members of the working group would include, Dr. Leroy Hood, President, Institute for Systems Biology; COL Craig D. Shriver, Director WRAMC Clinical Breast Care Project; F. Nicholas Jacobs, President and CEO Windber Research Institute; Dr. Edward Gorham, NHRC Special Programs Office; Mr. Kyle Martin, TATRC; and LTC G. Larry Maxwell, M.D., United States Military Cancer Institute." *(Draft version 3.0)*