UAMS

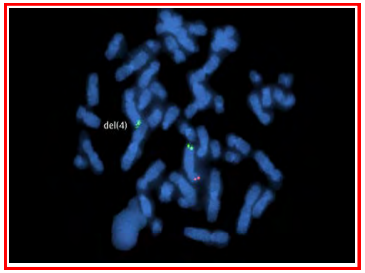
COLLEGE OF MEDICINE

UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES

UAMS College of Medicine Series

Showcase of Medical Discoveries:

A focus on Personalized Medicine



Wednesday,

September 4, 2013

4:00—5:30 p.m.

A Wine and Cheese Reception Featuring

UAMS Investigators Discussing

their Research and Discoveries.

Winthrop P. Rockefeller Cancer Institute 10th Floor Rotunda

Poster #1

Mapping the Cognitive Connectome: Translating Functional Neuroimaging into Personalized Medicine

Andrew James, PhD, Jennifer Fausett, Jennifer Gess, Tonisha Kearney-Ramos, Jennifer Peraza, Ashley Reno, John Greenfield, Clint Kilts

Our incomplete understanding of how the brain encodes cognitive variability remains the greatest barrier to translating functional neuroimaging into clinical practice. Neuroimaging studies have reported altered brain function for dozens of clinical disorders, but translating these findings into an individual patient's care requires a comprehensive mapping of individual variance in neurocognitive function for both healthy and clinical populations. To address this issue, we have developed the Cognitive Connectome – a comprehensive exploration of normative variability in cognition and brain function. The Cognitive Connectome is built from a battery of well-validated neuropsychological test and canonical functional MRI tasks spanning 8 cognitive modalities: motor, visuospatial awareness, attention, language, memory, affective processing, decision making, and executive function. Our pilot sample of 30 participants (mean±sd age= 32±10 years; 17 female; 11 African-American, 19 Caucasian) is allowing unprecedented insight into the nuanced interaction of brain and behavior. Our findings include a mapping of working memory's neural correlates and its hierarchical supervisory influence on other cognitive modalities and their brain networks; a demonstration of how personality factors influence the processing of novel emotional stimuli; and relating individual differences in cognition to individual differences in brain connectivity patterns. Clinical applications will emerge as this sample grows – i.e. predicting patient's treatment response from baseline brain scans or neurosurgical pre-planning to avoid cognitive impairment.

Poster #12

Predicting Heart Attacks in Women: Recognizing Early Symptoms

Jean McSweeney, PhD, RN, Mario Cleves, Ellen Fischer, Martha Rojo, Christina Pettey

Coronary heart disease (CHD) kills over 240,000 women in the U. S. annually. There is agreement that under-recognition of women's symptoms and difficulty in diagnosing their heart disease contribute to their greater disability and mortality. Coronary heart disease is treatable if detected early yet few questionnaires measure women's early warning prodromal symptoms (PS) of CHD. Many women report little or no chest pain prior to or during a heart attack. Thus, it is vital to identify women's symptoms other than chest pain associated with heart disease. However, no questionnaires assess other CHD prodromal symptoms that women report. The McSweeney Acute and Prodromal Myocardial Infarction Symptom Survey (MAPMISS) assesses 30 symptoms, weighted by severity and frequency; the scores are summed to create an overall symptom score. To assess the ability of the MAPMISS to predict women's CHD, women without heart disease that were referred to cardiologists in Arkansas participated. The MAPMISS questionnaire was administered to 1,097 women every three months for two years.

RESULTS: The prodromal score and symptoms were predictive of an event. Five symptoms were significantly associated with increased risk: discomfort in jaws/ teeth, unusual fatigue, arm discomfort, shortness of breath and generalized chest discomfort. Women reporting 1 or more of these symptoms were 4 times as likely to suffer a cardiac event. Both the MAPMISS PS scores and number of PS were significantly associated with cardiac events, suggesting specific symptoms can be easily assessed using the MAPMISS. This questionnaire could provide a predictive screen to assist clinicians in recognizing heart disease in women earlier.

Poster #11

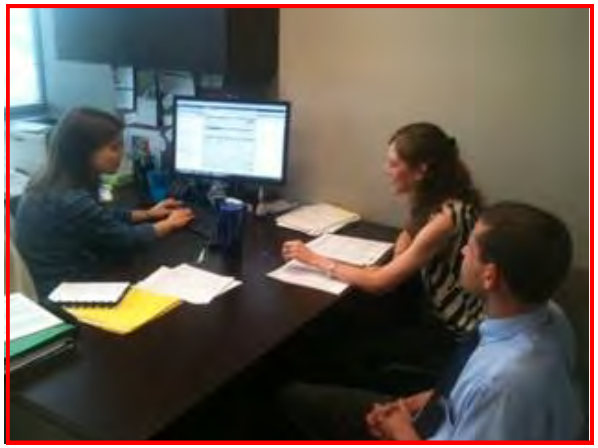
Interpretation and Meaning of Anti-HLA Antibodies Detected by Fluorescence Techniques

Terry Harville, MD

Determination of anti-HLA antibodies by fluorescence techniques is now the standard of practice, with assignment of a mean fluorescence intensity (MFI) based on its abundance and binding capacity in the patient serum. The goal is to use the anti-HLA antibodies for a "virtual crossmatch" for: (1) better patient-donor matching in organ transplantation, (2) determination of appropriate platelet donors, and (3) determining whether allele-specific antibodies may be pre-sent that can interfere with hematopoietic stem cell transplantation (HSCT). The assay is more sensitive than the previously utilized CDC (complement-dependent-cell-cytotoxicity) assay, with the unintended risk that a patient may be inappropriately predicted as incompatible. The overall aim of the study was to compare the results of a CDC crossmatch with the donor-specific anti-HLA anti-body (DSA) MFI values in order to determine which DSA are likely meaningful at specific MFI values. Results: MFI values <1000 correlated well with having a negative CDC crossmatch, but values >1000 correlated poorly (specificity 51%, PPV 38%, NPV 100%). These data indicate the use of 1000 MFI as the cutoff for positive detection of DSA will result in prediction of an unsuitable donor-patient virtual match ~62% of the time. Additionally, the newer fluorescence-based assays allow for detection of anti-HLA antibodies at the allele-level of discrimination. Anti-HLA antibodies can be divided into: (1) those which bind to a cell surface and activate complement, and thereby may be detrimental to endothelial cells in transplanted organs and (2) those which can bind to a cell sur-face, e.g., platelets, and directly exert a detrimental effect (without need for complement activa-tion). These results indicate that better techniques need to be developed for determination of truly detrimental DSA, in order to better discriminate appropriate donor-recipient pairing. The specific identification of anti-HLA antibodies directed against specific HLA allele products can allow for better HSCT donor selection, or the need for anti-HLA antibody reduction treatment prior to trans-plantation.

Poster #2

Personalized Medicine– Current Clinical Applications at UAMS



Jaime E. Vengoechea, MD, Jill Kelsay, MS, CGC,
and Lori Carpenter, MS, CGC

Examples of current applications of personalized medicine related to genetic conditions or genetic traits that can be seen in the UAMS Genetics clinic:

- Pharmacogenetics
- Clinical Genetics
- Cancer Genetics
- Ocular Genetics

Poster #3

Combining Proteomics and Gene Expression Profiling Identifies Seven Proteins/Genes Associated with Short Overall Survival in Multiple Myeloma

Rick Edmondson, MD
and Veronica
Macleod

While most patients with Multiple Myeloma have benefited from therapeutic advances, approximately 15% of patients have high risk disease with a poor prognosis. In this study, we combined gene expression profiling and proteomics to identify proteins/genes correlated with early disease-related death. Here, we report the first combined GEP and proteomics study of a large number of baseline samples (n=85) of highly enriched tumor cells from patients with newly diagnosed myeloma. Peptide expression levels from MS data on CD138-selected plasma cells from a discovery set of 85 patients with newly diagnosed myeloma were used to identify proteins linked to short survival (OS < 3 yrs vs. OS ≥ 3 yrs). The proteomics dataset consisted of intensity values for 11,006 peptides (i.e. 2,155 proteins), where intensity is the quantitative measure of peptide abundance; Peptide intensities were normalized by Z score transformation. Significance analysis of microarray (SAM) was applied resulting in 24 peptides identified as differentially expressed between the two groups (OS< 3 yrs vs. OS≥ 3 yrs), with fold change ≥1.5 and FDR <5%. The 24 peptides mapped to 19 unique proteins. All were at higher levels in the group with shorter overall survival than in the group with longer overall survival. An independent SAM analysis with parameters identical to the proteomics analysis (fold change ≥1.5; FDR <5%) was performed with the Affymetrix U133Plus2 microarray chip based expression data. This analysis identified 151 probe sets that were differentially expressed between the two groups (i.e., 144 probe sets at higher levels and seven at lower levels with shorter overall survival). Comparing the SAM analyses of proteomics and GEP data, we identified nine probe sets, corresponding to seven genes, with increased levels of both protein and mRNA in the short lived group. In order to validate these findings from the discovery experiment we used GEP data from a randomized subset of the TT3 patient population as a training set for determining the optimal cutpoints for each of the nine probe sets. Thus, TT3 population was randomized into two sub-populations for the training set (two-thirds of the population; n=294) and test set (1/3 of the population; n=147); the Total Therapy 2 (TT2) patient population was used as an additional test set (n=441). A running log rank test was performed on the training set for each of the nine probe sets to determine its optimal gene expression cutpoint. The cutpoints derived from the training set were applied to TT3 and TT2 test sets to investigate the groups' survival differences separated by the optimal cutpoint for each probe. Overall groups' survival was visualized using the Kaplan and Meier method and a P-value was calculated (based on log-rank test) to determine any statistically significant survival differences between the two groups (P≤0.05). Each of the seven protein/genes showed a significant association with survival in the validation sets.

Poster #10

Metabolomics Based Identification of Early Indicators of Liver Injury Due to Acetaminophen

Sudeepa Bhattacharyya, PhD, Lisa Pence, PhD, Rick Beger, PhD,
and Laura James, MD

Excessive use of acetaminophen, marketed as Tylenol, can cause fatal liver injury. Physicians can readily detect excessive acute use, as in a suicide attempt, but chronic overuse is frequently not recognized by physicians and/or patients. In previous work, we developed an assay (measurement of acetaminophen protein "adducts") that identifies liver injury due to acetaminophen. The assay reflects the known contribution of oxidative metabolism of the drug. Patients with acetaminophen overdoses and liver injury have very high serum levels of adducts, while patients that use acetaminophen as recommended by the manufacturer have very low, but detectable, se-rum levels of adducts and minimal liver injury. To better understand factors other than drug metabolism that contribute to the development of liver injury for the individual patient, we examined a large number of small molecules present in blood. Small molecule measurement, also known as "metabolomics", can be used to understand how some patients are more sensitive than others to a drug's particular effects (e.g., liver injury). Nine unique bile acid metabolites were examined in the blood samples of 18 patients hospitalized for treatment of liver injury secondary to acetamino-phen overdose. Bile acid metabolites were compared to standard clinical tests of liver injury (serum alanine aminotransferase or ALT) and to serum acetaminophen protein adduct levels during the hospitalizations. Elevations of bile acid metabolites occurred in the early stages of liver injury, in association with elevations of acetaminophen protein adducts. Importantly, both the bile acid metabolites and acetaminophen protein adducts were increased prior to the elevation of ALT, the standard clinical test for liver injury. The data suggest that bile acid metabolites and acetaminophen protein adducts are very sensitive indicators of liver toxicity due to acetaminophen overdose. In the future, this data can be used to identify subsets of patients that have increased susceptibility to liver injury from acetaminophen, thus allowing for the development of a personalized medicine approach focused on drug safety.

Poster #9

From Genome to Person– Data Integration for Personal Medicine

Mathias Brochhausen PhD, MA and William R. Hogan, MD, MS

In biomedical research and health care we store a vast amount of data for a multi-tude of purposes. Usually, data are captured to answer specific research questions or provide highly specific types of information. This shapes how the data look. The challenge in translational research is to access and integrate data about objects at different levels of granularity: we strive to create a more complete and deeper un-derstanding of how molecular processes shape the health of individual persons. On the way from the molecular perspective to the individual there are many intermedi-ate levels of granularity, such as, the cellular level, the tissue level, and the organ level. However, data about these levels is typically stored in ways that do not foster connecting knowledge about different granularity levels, or even spanning multiple levels of granularity.

A key aspect is to ensure that the same identifiers always refer to the same entities and the naming of entities does not vary between the granularity levels. To integrate and access the wealth of data existing, we need computer-interpretable models for diseases, proteins, genes, and procedures etc. that span the translational spectrum from molecule to population. Technologically, ontologies provide the means to help us with that task. Ontologies provide a hierarchy of the entities in a given domain along with both human-understandable and computer-interpretable definitions. There already exist a number of ontologies serving data annotation and integration purposes in biomedicine from genes to patients. Namely, the Open Biological and Biomedical Ontologies (OBO) Foundry provides a library of orthogonal biomedical ontologies, including, for instance, the Gene Ontology (GO), the Ontology of Bio-medical Investigation (OBI), and the Ontology of Medically Related Social Entities (OMRSE). We will show how these ontologies can be used to integrate biomedical and medical data spanning the entirety of translational science.

Poster #4

Focused Genome-Wide Analysis for Variants that Increase Risk for Chronic Kidney Disease

Ryan Farris, PharmD, PhD , Charla Wiley, and Elvin T. Price PharmD, PhD

Chronic kidney disease (CKD) occurs when the kidneys have become damaged and are no longer able to filter waste products from the blood. Waste product build up can lead to a range of symptoms affecting multiple organ systems. Since lifestyle changes and medications can slow CKD progression (i.e., delay or prevent kidney failure), early detection is vital. A major obstacle to early detection is that the initial stages of CKD are asymptomatic. Therefore, genetic approaches to identify variants, which increase CKD risk, may lead to earlier treatment and positively impact health outcomes. We conducted a genome-wide analysis of single nucleotide polymorphisms (SNPs), using Plink, in the nuclear receptor gene family to identify variants associated with CKD. Nuclear receptors regulate metabolic functions and many of these genes associate with disease states or syndromes that are either known CKD risk factors or increase mortality in CKD patients. This gene family is highly genetically variable between individuals. We hypothesized that probing these genes might lead to novel genetic variants and shine light on the pathophysiological processes involved. The data explored in our analysis was from an NIH sponsored study called the Hypertension Genetic Epidemiology Network (HyperGEN). The study had about 3400 participants, half of which were African-American, an overrepresented population in CKD patients and underrepresented in genomic studies. The phenotypes available for interrogation included, blood pressure, lipids, serum creatinine, fasting glucose, insulin, body mass index, and echocardiograms.

In our analysis, we stratified the participants into 4 groups: African-American males, African-American females, Caucasian males and Caucasian females. We identified different SNPs in each group with implications for renal dysfunction. In the African-American male group, we found a set of SNPs on chromosome 3 near the gene THRB with associations to worse diabetes status. In the African-American female group, we identified a set of SNPs on chromosome 5 near PPARGCB1 with associations to increased serum glucose levels. In the Caucasian groups, we found associations to increased serum creatinine levels, but in males the associated SNPs were on chromosome 3 near PPARg, while in females the SNPs were on chromosome 4, near PPARGCA1. Future work includes replicating these SNP associations in another study population.

Poster #5

Activation of Hallmark Pathways of Cancer in Patient Melanoma

Stephanie D. Byrum, Signe K. Larson, Nathan L. Avaritt,
Linley E. Moreland, Samuel G. Mackintosh,
Wang L. Cheung, and Alan J. Tackett, PhD

Molecular pathways regulating melanoma initiation and progression are potential targets of therapeutic development for this aggressive cancer. Identification and molecular analysis of these pathways in patients has been primarily restricted to targeted studies on individual proteins. Here, we report the most comprehensive analysis of formalin-fixed paraffin-embedded human melanoma tissues using quantitative proteomics. From 61 patient samples, we identified 171 proteins varying in abundance among benign nevi, primary melanoma, and metastatic melanoma. Seventy-three percent of these proteins were validated by immunohistochemistry staining of malignant melanoma tissues from the Human Protein Atlas database. Our results reveal that molecular pathways involved with tumor cell proliferation, motility, and apoptosis are mis-regulated in melanoma. These data provide the most comprehensive proteome resource on patient melanoma and reveal insight into the molecular mechanisms driving melanoma progression. Our studies are the initial steps for using proteomic approaches in a personalized medicine approach to treat melanoma.

Poster #8

Translational Pathology Shared Resource
Tissue Procurement Facility

Steven Post, PhD, Remelle Eggerson, BS, CRS,
and Mindy Gibbons, BSN, RNP

Advances in biomedical research, particularly in gene analysis and proteomics, have the potential to rapidly advance our understanding and treatment of diseases such cancer, Alzheimer's disease, heart disease, AIDS, multiple sclerosis, and a variety of others. Realizing this potential requires large numbers of human tissue samples with the associated clinical information linked to the tissue samples.

The UAMS Tissue Procurement Facility provides researchers with a high quality human biospecimen repository that uses best practices collection methodologies and appropriate clinical data capture mechanisms that maintain patient protection. Currently, the facility contains over 15,000 specimens of diseased and normal tissue linked with the associated de-identified clinical and pathological information maintained in a web-accessible, searchable database. The Tissue Procurement Facility is thus a valuable research resource for advancing our understanding of disease and translating this into improved patient care.

Poster #7

Use of Pharmacogenomics to Guide Treatment of Mood Disorders

Hunter Gibbs, MD, Ricardo Caceda, MD, PhD
and Jeffrey Clothier, MD

Major Depressive Disorder (MDD) occurs in 10-15% of the US population, at a cost of $83.1 billion annually. Current treatment protocols call for initiation of antidepressant medication with an adequate trial of 4-6 weeks completed prior to changing pharmacotherapy. Pharmacogenomics, while still in its infancy, promises to individualize the treatment of MDD. Here, we report our attempts to use a commercially available genetic assay in the individualization of pharmacotherapy for the treatment of refractory mood disorders.

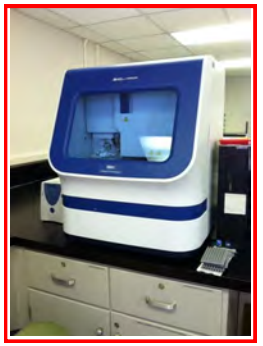
Methods: The Genecept™ Assay was performed on 21 individuals with treatment refractory mood disorder. The results of the assay were then used to determine appropriate pharmacotherapeutic interventions in order to improve symptoms and reduce side effects.

Results: The genetics assay was used to change the treatment course in 15 of 21 patients followed. In 14 of these patients, a positive clinical outcome was observed including improvement in symptomatology and side effects burden.

Conclusions: Genotype assays are useful in the individualization of pharmacotherapy for the treatment of MDD. Previously treatment refractory patients can experience clinical improvement with individualization of pharmacotherapy. Side effect profiles are also improved with individualization. At what point this assay can be cost-effective remains to be proven.

Poster #6

Precision Genomic Medicine in the Clinical Laboratory



William Bellamy, PhD, Jennifer Laudadio, MD, and Chuck Sailey, MD

The completion of the human genome project has provided a greater understanding of the genetic basis of disease and afforded the possibility for targeted, precision therapies to improve patient outcomes. The term “precision medicine” reflects the coupling of existing clinical-pathological parameters with state-of-the-art molecular profiling to create diagnostic, prognostic and therapeutic strategies precisely tailored to a patient’s individual needs and situation. The hallmark of this approach offers the right test or therapy at the right time and dose. Current applications are important in oncology where identification of specific alterations or mutations observed in an individual’s tumor is now used to direct very specific, targeted therapies. This includes the use of HerceptinTM in patients demonstrating amplification of ERBB2 (HER2), GleevecTM to target the BCR/ABL1 tyrosine kinase, and EGFR inhibitors (e.g., ErbituxTM) in patients demonstrating mutations in this gene, or conversely, the avoidance of EGFR inhibitors in patients with KRAS mutations. Besides somatic alterations, investigation of germ-line cancer predisposition markers has contributed to improved patient management in the diagnosis of Lynch Syndrome. As the number of known cancer markers increases, traditional methodologies examining one mutation at a time will no longer be effective either in terms of cost or tissue utilization. New technologies (Next-generation sequencing (NGS) strategies) that enable the sequencing of large amounts of DNA in parallel and at much lower costs than conventional methods are now being utilized in the clinical laboratory setting. NGS-based strategies have been broadly adopted by the biomedical research community for complex genomic analyses and are now moving into the clinical laboratory. While the most common clinical applications of NGS are in cancer testing, great potential exists for cost-effective testing in inherited disorders where there are numerous potentially affected genes and the overlap of symptoms between multiple syndromes makes diagnosis difficult. In addition to improved diagnostics, precision medicine is expected to herald a rapid acceleration in the identification and development of new pharmacotherapies and better utilization of existing agents through a better understanding of pharmacogenomics. NGS presents unique challenges for clinical laboratories ranging from the unprecedented data volume produced by the techniques, to determining how to appropriately validate these processes. Other aspects revolving around NGS include reimbursement issues and ethical concerns such as the discovery of sequence variants of unknown significance or the identification of clinically significant incidental findings. The Molecular Diagnostics Laboratory uses precision medicine to direct molecularly-targeted therapies in cancer and to expand into the arena of germline predisposition using colon cancer as the model. Studies have been initiated to bring increased pharmacogenomics testing to the Psychiatric Research Institute to help guide therapies of refractory patients. The UAMS Molecular Diagnostics Laboratory will play a leading role in expansion of the UAMS precision medicine initiative.