UAMS College of Medicine Series

Showcase of Medical Discoveries:

A focus on Rare Diseases

A Wine and Cheese Reception Featuring

UAMS Investigators Discussing

Their Research and Discoveries.

Winthrop P. Rockefeller Cancer Institute

10th Floor Rotunda

Wednesday, February 18, 2015

4:30—6:00 p.m.

Poster #1

What are Rare Diseases?

Patients, nonprofit support organizations and the scientific community work together to make research in rare diseases happen. Rare Disease Day, always on the 28th of February, is a day for the observance of research and advocacy work and the large amount of additional work still needed.

The poster "Rare Diseases and Their Research Stakeholders" provides:

- Diverse definitions of rare disease used around the globe
- Identities of rare disease research funders: e.g. NIH, PCORI and Foundations
- Rare disease advocacy groups that raise research funding and public awareness
- Historical background of research related public policy regarding rare disease and funding therapeutics research

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Poster #13

Resection and Hyperthermic Intrapleural Chemoperfusion for Recurrent Thymic Malignancy

Lu CK, Arnaoutakis K, Maraziti M, Gabel-Maraziti D, Steliga MA

Background: Thymomas are rare tumors with little randomized evidence to guide treatment. Surgical resection offers the best prognosis, however, recurrence can occur even after complete resection. Hyperthermic intrapleural chemoperfusion has been described as an adjunct to surgery in select cases with the hopes of providing increased local control beyond what could be accomplished with surgery alone. Our case is one example in which intraoperative hyperthermic chemotherapy was used. While the types of surgery may vary, the illustrated hyperthermic chemotherapy perfusion circuit has not been commonly described and may be adapted to different needs.

Methods: Patient is a 61 year old female with a history of thymoma who underwent surgical resection and adjuvant chemotherapy in 2011. She developed recurrence of her disease in 2013 and was referred for cytoreduction and concurrent intrapleural hyperthermic chemoperfusion. Following resection, a 24 Fr chest tube was placed in the apex of the chest for inflow, and two 24 Fr chest tubes were placed at the diaphragm bases for outflow. Hyperthermic intrapleural chemoperfusion with cisplatin (100mg/m2) was initiated for one hour at a rate of one liter per minute and at a temperature of 41-42 degrees Celsius.

Results: During the hyperthermic perfusion, patient experienced brief limited arrythmias with one episode of hypotension- systolic blood pressure in the mid-70s that persisted for less than one minute. She otherwise tolerated the procedure well with no perioperative complications. Patient was discharged home on post-operative day 5.

Conclusion: This single case demonstrates feasibility of intrapleural hyperthermic chemoperfusion for select intrathoracic malignancies. It is easy to perform, safe, appears to achieve high local control rates and survival benefit in thymic malignancies, and should be considered as part of the multimodality therapy for treatment of recurrent thymic malignancies.

Poster #2

Alpha-1 Antitrypsin Deficiency Community Members Describe Social Burdens: Informing Clinical Practices, Conceptual Framework & Psychometric Development in Rare Genetic Conditions

Pamela Holtzclaw Williams, JD, PhD, RN; Charlie Strange, MD; Natalie Dumont BS; Sara Wienke MS, CGC; Susan Flavin MSN, RN; Deirdre Walker, Lucinda Shore MS; Jim Quill, Marvin Sineath, Barbara Warner

Persons living with rare genetic conditions experience social impact related to the conditions' genetic etiology and rarity. This report describes thematic domains operationally defined as "social burden," identified through systematic qualitative analysis of self-report by persons living with alpha-1 antitrypsin deficiency (AATD). The aim is to identify and describe thematic domains of social impact experienced by persons living with a rare genetic condition (AATD) and their implications. A community based participatory research (CBPR) partnership of patients, community leaders, and scientists designed and conducted focus groups and interviews of patients and caregivers within AATD community. Partners conducted a systematic qualitative analysis using NVIVO 10 software to facilitate coding, audits, and create an analysis trail. An inductive approach to coding resulted in a final set of 5 sub-domains of impact attributed to the condition's rarity and 5 sub-domains of impact attributed to the condition's genetic etiology. The 10 sub-domains of impact and their abstracted definitions support the reference to them collectively as social burden. Social impact of living with AATD can be thematically categorized around the condition's genetic etiology and rarity. These thematic categories can now support item generation for future scale and psychometric development to quantify burden levels carried by individuals and communities.

Poster #3

New Genes Causing Osteoporosis and Brittle Bone Disease

Roy Morello, Milena Dimori, Sarah Zimmerman and Melissa Heard

In my laboratory, we study the function of novel genes, with a focus on those likely involved in bone formation, development, homeostasis and disease. We utilize standard genetic techniques to generate ubiquitous or tissue-specific gene mutations in the mouse and then, with the use of multi-disciplinary approaches, including those of cell biology, biochemistry and cell microscopy, we characterize the phenotype of these mice. The ultimate goal is to understand the function of the protein encoded by the novel gene and its functional network of interactions. We then try to translate what we learned from the animal model into relevant pathological aspects of human diseases that affect our skeleton.

We recently characterized the function of the *Crtap* gene, a member of a recently described family of genes. *Crtap* inactivation in mice causes dramatic low bone mass and a functional defect in bone forming cells, the osteoblasts. We showed that Crtap forms an intracellular complex with two enzymes and that this complex is essential for proper collagen synthesis. Importantly, type I collagen is an essential 'scaffolding' molecule that gives rigidity to our bones and its mutations in humans cause autosomal dominant Osteogenesis imperfecta (OI or brittle bone disease), a congenital disease characterized by recurrent frequent fractures. We identified *CRTAP* as the first gene whose mutations cause rarer, recessive forms of OI. Our discovery led the way to the more recent identification of several new genes causing less common forms of OI. Currently, we continue to study the function of the Crtap protein, including its potential contribution to extracellular matrix mineralization and mesenchymal stem cell homeostasis in the bone marrow.

Given the importance of Crtap in bone homeostasis and human disease, we have now started to characterize a novel but evolutionarily related gene, called Sc65. It encodes a protein highly similar to Crtap and we hypothesized that it may have retained a similar function. We generated mice that do not produce Sc65 protein and showed that they also have low bone mass. Current experiments are aimed at the identification of the cellular and molecular defects with the hope that these studies will provide us with novel biological insights into how bone is formed and maintained and how these processes can be affected in human skeletal disease.

Poster #12

Cholesterol-enriched diet alters hippocampal spine density and dendritic morphology in a murine model of familial hypercholesterolemia

Allen A.R.*, Anderson J.E., Farris R., Wang J., Palade P.T., Price E.T.

Familial hypercholesterolemia (FH) is an inherited metabolic disorder characterized by high levels of plasma low-density lipoproteins (LDL). FH patients have defective LDL receptors (LDLr) that impairs LDL metabolism resulting in significant risks of developing atherosclerosis. Epidemiological studies have shown that hypercholesterolemia is an early risk factor for Alzheimer's and FH patients exposed to higher cholesterol levels from early in life – may be considered high-risk for cognitive decline. One useful tool to study the impact of elevated circulating cholesterol levels on metabolic and functional parameters in different organs is the LDL receptor knockout mice (LDLr-/-), which represent a model of FH. A cholesterol-enriched diet (CED) causes these mice to develop severe hypercholesterolemia and substantial atherosclerosis. With respect to the brain, CED has been shown to induce specific hippocampal-dependent cognitive impairments that involve spatial learning and memory. Changes in synaptic plasticity underlie many neurodegenerative conditions that correlate to specific structural alterations in neurons that are believed to be morphologic determinants of learning and memory. To determine whether changes in dendritic architecture might underlie the neurocognitive sequelae following (FH) we investigated the impact of CED on a range of micromorphometric parameters in mice after 26 weeks of exposure.

Poster #11

Development of Novel ALS Mouse Model with Mutant Profilin1 for mechanistic and therapeutic studies

Shilpi Yadav, Michael Cozart, Awantika Singh, Cesar M. Compadre, Noel, Y., Calingasan, Flint M. Beal and Mahmoud **Kiaei**

Amyotrophic lateral sclerosis (ALS) is a devastating neuromuscular disease that is responsible for the death of 8,000 people per year in USA and 30,000 worldwide. In spite of its discovery 140 years ago, the pathogenic mechanism(s) causing selective motor neuron degeneration are still unknown and there isn't any cure or effective therapy for ALS. Additional animal models are required to further define pathogenic mechanisms of disease and facilitate development of novel therapies for ALS. Recently, five mutations in profilin1 (PFN1) gene (ALS18) were identified to be linked to a sub-population of fALS patients (Wu et al. 2012). PFN1 is a ubiquitously expressed small protein and interacts with over 50 ligands and classically known as regulator of actin polymerization. Mutant profilin1 may induce neurotoxicity leading to motor neuron degeneration in mice. Our goal is to understand how mutant PFN1 causes neurodegeneration and identify drugs that can block it. We developed transgenic mice with ALS-like disease phenotypes to investigate the mechanism(s) of mutant PFN1 neurotoxicity and test therapeutic strategies for development of therapy for ALS.

Supported by COBRE (P20 GM103425-10 and P30 GM 110702)
Wu, C. H. et al. (2012). Nature 488(7412): 499-503.

Poster #4

Clinical trials of HIV-related Kaposi's Sarcoma - the AIDS Malignancy Consortium Experience

Jeannette Y. Lee, Ph.D., Page Moore, Ph.D. Stephen Erickson, Ph.D. and Shelly Lensing

Kaposi's Sarcoma (KS), the most common malignancy associated with HIV, is characterized by skin lesions and may include tumor-associated edema and/or visceral disease. This presentation summarizes clinical trials to treat KS conducted by the AIDS Malignancy Consortium over its 20-year history.

Poster #5

Assessing the role of BB0345 during Borrelia burgdorferi mammalian infection

Jon Blevins, Ph. D.

Pathogens of the genus *Borrelia* are spirochetal bacteria transmitted to humans via the bite of an infected arthropod. There are two infections, Lyme disease and relapsing fever, which are commonly associated with *Borrelia* infection. Lyme disease presents with numerous chronic manifestations, including rheumatologic, neurological, and cardiac abnormalities. Humans develop Lyme disease after becoming infected with *B. burgdorferi,* which is transmitted via the bite of *Ixodes sp.* hard ticks. In contrast, relapsing fever is an acute infection presenting as recurring episodes of fever, aches, and nausea with each episodes of fever being associated with bacteremia. In the United States, relapsing fever is caused by three species of *Borrelia* that are each transmitted by *Ornithodoros sp.* soft tick.

Despite intensive research efforts studying the *Borrelia* that cause Lyme disease and relapsing fever, there is still significant progress to be made towards understanding pathogenic mechanisms that these bacteria utilize to cause disease, colonize tick vectors, and transmit during tick feeding. Specifically, we are working to determine how *Borrelia* controls the expression of its genes as it moves between tick and mammal and define contributions of individual *Borrelia* genes to bacterial virulence and tick colonization. One of the most direct approaches to demonstrate a causal relationship between a bacterial gene, its cognate gene product, and a requirement during the bacterial lifecycle is to create *Borrelia* strains in which specific genes of interest have been inactivated. The abilities of these mutant strains to colonize animals and ticks can then be assessed experimentally to determine whether a given mutant is no longer competent for infection. Once bacterial factors required for *Borrelia* infection or tick transmission have been identified, we can begin to study their physiological contributions to these bacterial processes. In addition, since these factors are known to be essential during the bacterial lifecycle, they also represent viable targets against which therapies could be developed to prevent or treat disease.

Poster #10

Natural history study of patients with arterial tortuosity syndrome

Tiffany Lepard Tassin, M.S., C.G.C.

Arterial tortuosity syndrome (ATS) is a rare connective tissue disorder, characterized by elongation and tortuosity of mid and large sized arteries. Little is known of the natural history of ATS. The purpose of this study is to evaluate the natural history of disease progression and further clarify the phenotype of ATS. This is a descriptive, retrospective and longitudinal five-year chart review study of patients with ATS. Twelve patients are currently enrolled in the study and retrospective data has been collected. There are currently no management or screening guidelines for ATS. Knowledge gained from this study can contribute to the creation of these guidelines and ultimately improve the health of individuals with ATS.

Summary**:** Very little is known about arterial tortuosity syndrome, a rare connective tissue disorder. Through this study, we hope to further clarify the disorder and disease progression.

Poster #9

Sickle Cell Disease in Pregnancy

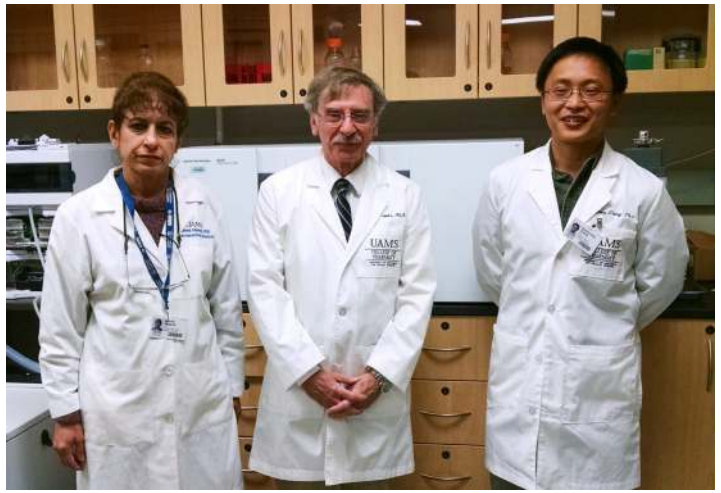
ANGELS®

Jonathan Chang, MD; Sarah Rhoads Kinder, PhD, DNP, APRN; Hari Eswaran, PhD; Amit Saha, MS; Heath Gauss, MS and Everett Magann, MD

Sickle cell disease (SSD) in the United States (US) affects between 90,000-100,000 people, primarily of African American descent. Sickle cell disease is inherited in an autosomal recessive pattern. Pregnant women with SSD are not only predisposed to complications specific to SSD, but also issues unique to pregnancy. Due to anemia prior to pregnancy and associated with pregnancy, these women often require multiple blood transfusions. Another concern of SSD is pulmonary hypertension which becomes significant during pregnancy. Due to the increased cardiopulmonary demands of pregnancy, women with pre-existing pulmonary hypertension have a 16% mortality rate. These women are also more likely to develop pre-eclampsia and eclampsia. In the US alone, maternal mortality rates are 10 times higher in individuals with SSD than in those without SSD. Fetal morbidity is secondary to uteroplacental insufficiency, possible alloimmunization from transfusions, and chronic opioid exposure. Because of the significant morbidity and mortality related to the disease, SSD in pregnancy leads to an increased number of hospitalizations, increased length of stay, increased medical costs, increased neonatal intensive care unit stay, and worse maternal and neonatal outcomes. The purpose of this study is to examine rates of SSD in pregnancy, pregnancy outcomes and neonatal outcomes in Arkansas.

Poster #6

Valchlor: An Approved FDA Drug for Treatment of Mycosis Fungoides, Cutaneous T-cell Lymphoma

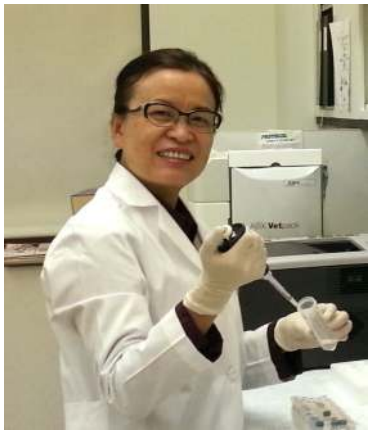


Zaineb AF Albayati, Abeer M Al-Ghananeem, Vipin P Nair, Sundar Neelakantan, David R Worthen, Guangrong Zheng, Marhaba Hojahmat and Peter A Crooks

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma, a rare form of non-Hodgkins lymphoma. It has no cure, and its cause is unknown. The malignant T-cells migrate to the skin, causing lesions to appear. Lesions first appear as a rash and then may grow into disfiguring tumors. MF is an uncommon disease, with an incidence of less than 1 per 100, 000 person-years in the U.S.A. The low incidence of disease makes clinical studies more challenging. Valchlor, a topical formulation of mechlorethamine is a breakthrough medicine for the intervention of stage 1A and 1B mycosis fungoides-type cutaneous T-cell lymphoma. Valchlor is formulated in a unique way to chemically stabilize mechlorethamine and keep it from entering a patient's bloodstream. Topical application of Valchlor in patients with MF has shown that 60% of patients demonstrated 50% improvement and 48% of Valchlor-treated patients achieved complete skin remission of their skin lesions within 1-12 months of treatment. In summary, Valchlor is the first and only FDA-approved topical formulation for the topical treatment of MF cutanous T-cell lymphoma.

Poster #7

miR-183 Over-expression: A Potential Biomarker for Juvenile Myelomonocytic Leukemia (JMML)



Y. Lucy Liu[1], Yan Yan[1]*, Shelly Y. Lensing[2]*, Todd Cooper[3], and Peter D. Emanuel[1]

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Juvenile myelomonocytic leukemia (JMML) is a rare disease of early childhood with extremely high monocytes in peripheral blood(PB). The pathogenesis of JMML is linked to dysregulated NF1/RAS signaling pathway that is partially caused by genetic mutation of *Ras*, *PTPN11,* and *c-CBL*, or loss-of heterozygosity of *Nf1*. The hallmark of JMML cells is selectively hypersensitive to GM-CSF *in vitro*. We previously reported that protein deficiencies of PTEN, CREB, and Egr-1 were frequently observed in JMML (67-87%). Recent research indicated that *Egr -1* was targeted by miR-183. We hypothesized that microRNAs may play an important role in contributing to the deficiency of *Egr-1*. Using relative-quantitative real-time PCR, we found that the median level of miR-183 was significantly higher in 47 JMML mononuclear cells in comparison to controls ($p<0.001$). We further analyzed the correlation between the expression level of miR-183 and the monocyte percentage in PB. Strikingly, there was a significant correlation between the expression level of miR-183 and the monocyte percentage in PB from 34 patients ($p<0.05$). This is the first evidence suggesting that microRNAs contribute to the pathogenesis of JMML. miR-183 may also serve as an important biomarker for JMML. It may ultimately provide a target for JMML therapy.

Poster #8

Rare Diseases: Making the Best Use of Sparse Data

M. Brochhausen, B. Jiang, A. Hicks, and U. Topaloglu

In the US, a disease is a rare disease if it affects less than 200,000 patients. Hence, one of the most pressing problems regarding research on rare diseases is the scarcity of available data. Therefore, in rare disease research the need to extract the best quality of information from the existing data is even more pronounced than in biomedical research in general. One factor that adds to the problems created by the scarcity of data is the fact that in biomedical and clinical research data are seldom captured using the same data schema or data representation.

One strategy to tackle problems created by data that is captured or stored heterogeneously is using ontologies as a shared representation of data. Ontologies are formal, computable representations of an area of interest. Ontologies cannot only help with integrating data from heterogeneous data sources; they can provide computable representations of textbook knowledge to support researchers in tackling the data that they have access to. The first comprehensive ontology for rare diseases has just been released in Europe: The Orphanet Rare Disease Ontology (ORDO).