Proceedings

36th Annual Meeting
Texas Genetics Society

A forum for young geneticists to present their research

featuring

The Barbara H. Bowman Award Winner for 2009

Richard Gibbs, Ph.D.

April 2 – 4, 2009

Wyndham Garden Hotel and Woodward Conference Center

Austin, Texas

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Welcome

I want to welcome you to the 36th Annual Meeting of the Texas Genetics Society.

The Texas Genetics Society was established in 1974 as a nonprofit association whose purpose is to foster the development of all aspects of genetics, to promote the exchange of research results and the teaching of genetics, and to provide a forum for discussion of matters of interest to all geneticists. Membership is open to all persons interested in genetics research, the training of geneticists, and the delivery of genetic services.

By design, this meeting includes a wide range of topics in genetics. The intent is to provide a venue for genetics students and young faculty from Texas at all levels in their training to present their research in a collaborative environment.

The goals of the meeting are to bring together geneticists from around Texas to discuss current trends in genetics, to foster collaborative research opportunities for established scientists, and to create training opportunities for students and postdoctoral fellows. At the conclusion of this meeting, we anticipate that our scientific networks will have expanded, including establishment of new connections, for our genetics research.

The officers and Board members wish to thank each of the registered participants for joining us this year. We are most appreciative of the invited speakers and session chairs for accepting our invitation and special thanks is due Dr. Rodney Nairn for handling the local arrangements in Austin.

We look forward to excellent presentations by the speakers and poster presenters, and to lively discussions and interactions at the formal sessions and at the social events. Have a fun-filled and productive experience.

On behalf of the Executive Committee,
Loren C. Skow

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(979) 845-3194

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(512) 477-1972

Student/Post-doc/Technician
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Texas A&M University, College Station
jlb6736@neo.tamu.edu
(409) 880-5579

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(214) 559-7861
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(979) 845-2616

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Rkrahe@mdanderson.org
Center (713) 834-6345

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robert.bradley@ttu.edu

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akillary@mdanderson.org
(713) 792-7833

Karen Vasquez 2008-2011
University of Texas M.D. Anderson Cancer Center, Smithville.
kvasquez@mdanderson.org

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Program
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Local Arrangements 2009
Rodney Nairn

Awards
Charleen Moore (chair), Rodney Nairn and Bhanu Chowdhary

Nominating
Heather Conrad-Webb, Terje Raudsepp, and Brenda Rodgers

The Organizing Committee wishes to thank the following companies and representatives, whose support was essential to the success of this meeting.

Applied Biosystems, a part of Life Technologies	Richard Brooks
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Scientific Program

36th ANNUAL MEETING OF THE TEXAS GENETICS SOCIETY

April 2-4, 2009
Austin, Texas

Thursday, April 2

5:00 - 7:00 pm **Registration** – Foyer.

5:30 - 7:00 pm **Opening Reception** - Lake LBJ.

7:00 - 8:00 pm **Keynote Address** – Dr. Jaquelin Dudley, University of Texas, Austin. **Genetics of mouse mammary tumor virus: Implications for cancer and infectious disease.** Lake Austin/Lake Travis.

Friday, April 3

7:30 - 8:30 am **Late Registration and Continental Breakfast** – Foyer and Lake LBJ.

8:30 - 8::35 am **Welcome & Announcements** – Lake Austin/Lake Travis.

8:35 - 9:30 am **Invited Address** – Dr. Alex Pertsemlidis, McDermott Center for Human Growth and Development,UT Southwestern Medical Center. **Killing the messenger (RNA): microRNA regulation in lung cancer.** Lake Austin/Lake Travis.

Contributed Papers Session I – Lake Austin/Lake Travis

9:30 - 9:45 am **Suppression of bovine and caprine myostatin expression in vitro using RNA interference.** K. Tessanne[1], M. Golding[2], C. Long[1], and M. Westhusin[1]. [1]Texas A&M University, College Station, Texas, U.S.A., [2]University of Western Ontario, London, Ontario, Canada.

9:45 - 10:00 am **Structural and expression analyses of a segmental duplication within the equine lymphocyte antigen.** C.L. Brinkmeyer-Langford[1], W.J. Murphy[1], C.P. Childers[2], L.C. Skow[1]. [1]Department of Veterinary Integrative Biosciences, Texas A&M University, College Station, TX, [2]Department of Biology, Georgetown University, Washington, DC.

10:00 - 10:15 am **Sequence-dependent prion protein conversion: lessons from rabbits, mice and hamsters.** Marco A. Morales-Garza[1], Sergio Casas-Tinto[1], Yan Zhang[1], Melisa Gómez-Velazquez[1], Wen-Quan Zou[2], Pedro Fernandez-Funez[1] and Diego E. Rincon-Limas[1]. [1]Department of Neurology, UTMB, Galveston, TX; [2]Case Western Reserve University, Cleveland, OH.

10:15 – 10:30 am **Mapping a gene responsible for natural resistance to Rift Valley Fever Virus in inbred rats.** C. M. Busch, R. J. Callicott, and J. E. Womack. Dept. of Veterinary Pathobiology, Texas A&M University, College Station, TX.

10:30- 11:00 am **Coffee Break and Exhibitors** –Lake LBJ.

Contributed Papers Session II – Lake Austin/Lake Travis**.**

11:00 - 11:15 am **STAC3 found upregulated at tick attachment site in calves resistant to Amblyomma americanum infestation.** J.L. Butler[1], P.K. Riggs[2], P.J. Holman[1]. Departments of Veterinary Pathobiology[1], College of Veterinary Medicine and Animal Science[2], Texas A&M University, College Station, TX.

11:15 - 11:30 am **Haplotype structure of the bovine major histocompatibility. complex** Krista L. Fritz[1], Robert D. Schnabel[2], Jeremy F. Taylor[2], John C. Huber[1], Clare A. Gill[1], Marian L. Cothran[1], Renuka Chowdhary[1], Loren C. Skow[1]. [1]Texas A&M University, College Station, TX.; [2]University of Missouri, Columbia, MO.

11:30 - 11:45 am **Stallion fertility: Are Y-linked genes involved?**
Nandina Paria, Sankar P. Chaki, Bhanu P. Chowdhary and Terje Raudsepp Department of Veterinary Integrative Biosciences, Texas A&M University, College Station, TX.

11:45 am - noon **Linkage mapping of the harlequin locus in the Great Dane.**
K.L. Tsai[1], L.A. Clark[1], A.N. Starr[2], K.E. Murphy[2]. [1]Dept. of Veterinary Pathobiology, Texas A&M Univ., College Station, TX.; [2]Dept. of Genetics and Biochemistry, Clemson Univ., Clemson, SC.

12:00 - 1:30 pm **Workshop and Lunch.**

1:30 - 2:30 pm **Invited Address** – Dr. Monique Rijnkels, Baylor College of Medicine.
Epigenetic changes during functional differentiation of the mammary gland.

Contributed Papers Session III – Lake Austin/Lake Travis.

2:30 - 2:45 pm **Loss of function mutations in angiopoietin-like proteins (ANGPTLs) contribute to plasma triglyceride levels.** W. Yin, S. Romeo, H.H. Hobbs, and J.C. Cohen. McDermott Center for Human Growth and Development and the Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, TX.

2:45 – 3:00 pm **The ER stress transcription factor XBP1s protects against amyloid-beta neurotoxicity**. Yan Zhang, Sergio Casas-Tinto, Melisa Gomez-Velazquez, Marco Morales-Garza, Diego E. Rincon-Limas and. Department of Neurology, University of Texas Medical Branch, Galveston, TX.

3:00 - 3:15 pm **Novel mitochondrial disease resulting from an ANT2 null human.** Jaeckle Santos, L.J., Baker, L.A., Garg, V., and Zinn, A.R. University of Texas Southwestern Medical School at Dallas, TX.

3:15 – 3:45 pm **Coffee Break.**

Contributed Papers Session IV – Lake Austin/Lake Travis

3:45 – 4:00pm **Evolutionary constraints and the gene expression pattern of duplicated genes of the *Rhodobacter sphaeroides* 2.4.1.** Lin Lin, Kristen Schroeder, Anne Peters, and Madhusudan Choudhary. Department of Biological Sciences, Sam Houston State University, Huntsville, TX.

4:15 - 4:30 pm **The mismatch repair heterodimer MutSβ, and the nucleotide excision repair protein complexes, XPA-RPA and XPC-RAD23B interact on DNA interstrand crosslinks**. Junhua Zhao[1], Aklank Jain[1], Ravi R. Iyer[2], Paul L. Modrich[2], and Karen M. Vasquez[1]* [1]Department of Carcinogenesis, The University of Texas M. D. Anderson Cancer Center, Smithville, TX and [2]Department of Biochemistry and Howard Hughes Medical Institute, Duke University Medical Center, Durham, NC.

4:30 – 4:45 pm **Development of novel methods to detoxify sulfur mustard gas using a nucleophilic agent.** Stephen Boulware, Michael C. MacLeod, and Karen M. Vasquez. Department of Carcinogenesis, The University of Texas M.D. Anderson Cancer Center, Science Park-Research Division, Smithville, TX.

4:45 – 5:30 **Board meeting**

5:30 - 7:00 pm **Reception and Poster Viewing** – Lake LBJ

7:00 - 9:00 pm **Banquet and 2009 Meeting Awards** . **Barbara Bowman Award**.
Dr. Richard Gibbs, Director, Human Genome Sequencing Center, Baylor College of Medicine. **Please don't tell my grandmother I am a geneticist: She thinks I am a piano player in a honky-tonk.** Lake Austin/Lake Travis.

Saturday, April 4

7:30 - 8:30 am **Continental Breakfast** – Foyer/Lake LBJ

8:30 - 8:35 am **Announcements**

8:35 - 9:30 am **Invited Address –** Dr. Trey Fondon III. University of Texas at Arlington. **Slippery genomes: Investigating the role of tandem repeats in evolutionary plasticity.**

Contributed Papers Session V – Lake Austin/Lake Travis

9:30 - 9:45 am **Cruciform-forming inverted repeats mediated microinversions that distinguish the human and chimpanzee genomes.** Albino Bacolla[1], Jessica Kolb[2], Nadia A. Chuzhanova[3], Josef Högel[2], Karen M. Vasquez[1], David N. Cooper[4] and Hildegard Kehrer-Sawatzki[2]. [1]Department of Carcinogenesis, The University of Texas M.D. Anderson Cancer Center, Smithville, TX. [2]Institute of Human Genetics, University of Ulm, Albert-Einstein-Allee 11, Ulm, Germany. [3]School of Computing, Engineering and Physical Sciences, University of Central Lancashire, Preston, UK. [4]Institute of Medical Genetics, School of Medicine, Cardiff University, Cardiff, UK.

9:45 - 10:00 am **Use of a Werner knockdown cell line to investigate the role of WRN in mammalian recombination**. Jennifer J. Rahn, Luis Della-Coletta, Megan Lowery, Tiffany Limanni, Gerry M. Adair, Rodney S. Nairn. Department of Carcinogenesis, Science Park Research Division, UT MD Anderson Cancer Center, Smithville, TX

10:00 - 10:15 am **A conditional mouse model for assessing BLM in homologous recombination.** A.D. Brown[1] and A.J.R. Bishop[1,2]. [1]Department of Cellular and Structural Biology, [2]Greehey Children's Cancer Research Institute, The University of Texas Health Science Center at San Antonio, San Antonio, TX.

10:15 - 10:45 am **Coffee Break and Judges' Meeting** – Foyer and Lake LBJ

10:45 - 11:45 **Business Meeting** – Lake Austin/Lake Travis

11:45 am **Adjourn**

Abstracts

Abstract 1 - Contributed Paper

Suppression of bovine and caprine myostatin expression *in vitro* using RNA interference.

K. Tessanne[1], M. Golding[2], C. Long[1], and M. Westhusin[1]. [1]Texas A&M University, College Station, TEXAS, [2]University of Western Ontario, London, Ontario, Canada.

RNA interference (RNAi) is a means of regulating gene expression by targeting mRNA in a sequence-specific manner for degradation or translational inhibition. Short hairpin RNAs (shRNAs) and siRNAs have been extensively employed for manipulating gene expression in a wide range of species. Our goal in this study was to develop a repeatable and reliable method for inducing an RNAi-based suppression of myostatin expression in livestock species. Myostatin, or growth differentiation factor 8 (GDF8), is a negative regulator of skeletal muscle mass. The most notable effect of a mutation in this gene is a double-muscling phenotype due to both hypertrophy and hyperplasia of muscle fibers. To test the effectiveness of the RNAi based approach, DNA constructs expressing short hairpin RNAs (shRNAs) targeting homologous sequences of both caprine and bovine myostatin mRNA were cloned into a lentiviral plasmid containing an EF1α promoter and a GFP reporter. These plasmids were transfected into a genetically modified HEK 293T cell line expressing caprine myostatin mRNA. Transfection efficiency averaged 60% throughout the study. Analysis by real-time quantitative PCR revealed caprine myostatin mRNA suppression ranging from 45%-70% as compared to a nonsense shRNA control, and this indicated a significant reduction in myostatin mRNA levels given the transfection rates. Additional research is currently underway utilizing bovine primary fetal muscle cells. In this study, we will utilize lentiviral vectors to compare constitutive expression of the most effective shRNAs (identified above) with a new vector engineered to express the same shRNAs via a muscle-specific myogenin promoter. Off-target effects and toxicity from lentiviral-mediated delivery of shRNAs into animals has been documented. Therefore, tissue-specific expression of targeting shRNAs would decrease the potential for these effects. The production of transgenic animals exhibiting myostatin knockdown through lentiviral mediated RNAi will not only demonstrate the utility of RNAi in the study of gene function in large animal models, but may also provide a valuable model for studying muscle regeneration and repair.

Classification: Graduate Student

Abstract 2 - Contributed Paper

Structural and expression analyses of a segmental duplication within the equine lymphocyte antigen.

C.L. Brinkmeyer-Langford[1], W.J. Murphy[1], C.P. Childers[2], L.C. Skow[1]
[1]Department of Veterinary Integrative Biosciences, Texas A&M University, College Station, TEXAS 77843,
[2]Department of Biology, Georgetown University, Washington, DC 20057

The horse major histocompatibility complex (MHC) (also termed equine lymphocyte antigen, ELA) bears a strong similarity in organization and gene content to the MHCs of most other mammals. Comparison of MHC gene content and order between the horse and human genome sequences predictably showed a great deal of similarity between the two, with two notable exceptions: a gene desert between the ELA class II and class III regions and a segmental duplication at the boundary of ELA class I and class III. The segmental duplication consists of a ~900 Kb region that contains at least 11 duplicated units: ten consisting of a class I-like gene and the helicase domain part of a BAT1-like gene, and one which harbors the full-length BAT1 gene. Evidence of this feature was found in the genomes of other Perissodactyls and has been previously reported in cats. *In silico* as well as PCR analyses suggested that it is not present in other mammalian species. Preliminary reverse-transcriptase PCR (RT-PCR) studies using both healthy and immune-stimulated horses have shown that several of these duplicated segments contain transcribed open reading frames. Evidence of alternative splicing and differential expression hints at possible species- or order-specific roles for this segmental duplication; as both genes are involved in immune function, this could elucidate a novel response mechanism.

Classification: Postdoc

Abstract 3 - Contributed Paper

Sequence-dependent Prion Protein conversion: lessons from rabbits, mice and hamsters.

Marco A. Morales-Garza[1], Sergio Casas-Tinto[1], Yan Zhang[1], Melisa Gómez-Velazquez[1], Wen-Quan Zou[2], **Error! Reference source not found.**[1] and Diego E. Rincon-Limas[1].
[1]Department of Neurology, UTMB, Galveston, Texas, U.S.A.; [2]Case Western Reserve University, Cleveland, Ohio, U.S.A.

Prion diseases are incurable neurodegenerative disorders in which the normal cellular prion protein (PrP^{C}) converts into a misfolded isoform (PrP^{Sc}) with distinct biochemical and structural properties. The unique feature of the spongiform encephalopathies is its transmissibility, where normal PrP^{C} converts to pathogenic PrP^{Sc} by unknown mechanisms. Many mammalian species have shown their susceptibility to prion diseases, including human, cow, sheep, goat, mouse, hamster, and deer; however, rabbits have proven resistant to many prion strains in nature and in the lab, and the reason for this is still a mistery. We reasoned that this unusual and intriguing phenomenon could help us understand the rules governing PrP conversion and pathogenesis. To evaluate the contribution of the primary sequence in PrP conversion, we first generated transgenic flies expressing rabbit PrP (RbPrP) in brain neurons. Then, we compared the neuropathological properties of RbPrP with those of transgenic flies expressing PrP from mouse (MoPrP) and hamster (HaPrP) at similar levels. Mice and hamsters are two traditional models in prion biology and both are highly susceptible to prion infectivity; however, the hamster is preferred because of the particular ferocity of the disease. Interestingly, we observed that these three prion proteins display dramatically distinct behaviors in flies. While HaPrP is highly pathogenic in the brain, RbPrP is not and MoPrP seems to present a mild phenotype. Our data demonstrate that a few amino acid substitutions in the PrP sequence are key for disease susceptibility. Thus, our results suggest that molecules with rabbit –specific residues could act as anti-prion compounds.

Classification: Postdoc

Abstract 4 - Contributed Paper

Mapping a gene responsible for natural resistance to Rift Valley Fever Virus in inbred rats

C. M. Busch, R. J. Callicott, and J. E. Womack
Dept. of Veterinary Pathobiology, Texas A&M University, College Station, TEXAS

The Rift Valley Fever virus (RVFV), a phlebovirus which presents an epidemic and epizootic threat in sub-Saharan Africa, Egypt, and the Arabian Peninsula, has recently gained attention as a potential weapon of bioterrorism due to its ability to infect both livestock and humans. Inbred rat strains show similar characteristic responses to the disease as humans and livestock, making them a suitable model species. Previous studies have shown differences among various inbred rat strains in susceptibility to RVFV hepatic disease, including a higher susceptibility of Wistar-Furth (WF) rats compared to the more resistant Lewis (LEW) strain. Further study revealed that this resistance trait follows the pattern of a dominant gene inherited in Mendelian fashion. A congenic WF.LEW strain resistant to infection with RVFV was derived from the susceptible WF and resistant LEW strains, and a subsequent genome scan of this congenic strain revealed two prospective regions for the location of the gene, one on chromosome 3 and the other on chromosome 9. Through backcrossing, genotyping, and subsequent challenges of three N1 litters with RVFV, the ~2MB region on the distal end of chromosome 3 was determined to contain the gene conferring resistance. Markers have been developed to detect recombination within this region of chromosome 3 and will be used on future backcross generations in conjunction with the RVFV challenges to narrow down the prospective region and facilitate identification of a candidate gene.

Classification: Graduate Student

Abstract 5 - Contributed Paper

STAC3 found upregulated at tick attachment site in calves resistant to *Amblyomma americanum* infestation.

J.L. Butler[1], P.K. Riggs[2], P.J. Holman[1]. Departments of Veterinary Pathobiology[1], College of Veterinary Medicine and Animal Science[2], Texas A&M University, College Station, Texas, U.S.A.

Ticks and tick-borne diseases, such as anaplasmosis, theileriosis, babesiosis, and heartwater, have drastically affected the livestock industry worldwide resulting in production loss, morbidity and mortality of cattle, and monetary losses that total billions of dollars to cattle producers across the globe. Although breed-associated differences in susceptibility to tick infestation have been documented for more than 50 years, the genetic mechanisms controlling natural host resistance are unknown. To identify genes important to natural resistance in cattle, microarray analysis of RNA isolated from tick bite site skin biopsies of calves phenotyped as resistant or susceptible to tick infestation was performed. The samples were collected at USDA–ARS, Kipling Bushland U.S. Livestock Insect Research Laboratory in Kerrville, TEXAS from a mixed-breed herd in which individual calves were phenotyped for resistance to the Lone Star Tick, *Amblyomma americanum* by exposure to two tick infestations. Total RNA extracted from tick-resistant and susceptible skin biopsies collected on day 7 of the second *A. americanum* infestation was used to generate microarray data. Analysis of these data revealed nine genes of immunological importance demonstrating a 3-fold or greater difference in expression between the resistant and susceptible calves. Samples from days 2, 3, and 5, also from the second tick exposure, were included with day 7 samples for subsequent real-time qRT-PCR analyses. Real-time qRT-PCR demonstrated that one of the 9 genes from the array data, STAC3, was upregulated in the calves exhibiting natural resistance, and therefore, may be associated with signaling pathways of the inflammatory immune response during tick infestation.

Classification: Graduate Student

Abstract 6 - Contributed Paper

Haplotype Structure of the Bovine Major Histocompatibility Complex.

Krista L. Fritz[1], Robert D. Schnabel[2], Jeremy F. Taylor[2], John C. Huber[1], Clare A. Gil1[1], Marian L. Cothran[1], Renuka Chowdhary[1], Loren C. Skow[1]
[1]Texas A&M University, College Station, TEXAS, 77843-4458, U.S.A.
[2] Division of Animal Sciences, University of Missouri, Columbia, MO, 65211-5300, U.S.A.

The major histocompatibility complex (MHC) is one of the most gene dense and polymorphic regions of the mammalian genome. More diseases have been associated with the MHC than any other genomic region, including most known autoimmune conditions. In this project, polymorphic markers spanning regions of the bovine MHC (BoLA) were used to characterize patterns of genetic variation and haplotype structure within a variety cattle breeds. Knowledge of BoLA haplotypes may be applied to marker assisted selective breeding of animals with superior disease resistance and productivity, as well as improved vaccine development for livestock in the future.

Classification: Graduate Student

Abstract 7 - Contributed Paper

Stallion fertility: Are Y-linked genes involved?

Nandina Paria, Sankar P. Chaki, Bhanu P. Chowdhary and Terje Raudsepp
Department of Veterinary Integrative Biosciences, Texas A&M University, College Station, TEXAS-77843, U.S.A.

Stallion fertility is an important economic trait in equine industry. Since horses are selected mainly for pedigrees and athletic performance, less attention has been paid to improve reproduction related traits. This is probably the reason why almost 35% of breeding stallions are qualified as subfertile and do not pass tests for breeding soundness. Therefore, stallion subfertility is of serious concern for breeders and owners.

Environmental factors affecting fertility and breeding physiology of stallions, especially sperm attributes, have been intensively studied. In contrast, the genetics of stallion fertility is still poorly understood. In mammals male fertility genes are distributed genome wide - both on autosomes and the sex chromosomes. Among the latter, as revealed from human and mouse studies, the small, gene-poor and male specific Y chromosome is particularly enriched for genes related to spermatogenesis and other male functions. However, direct association between Y-linked genes and male fertility has been so far demonstrated only in human and mouse. Therefore, the goal of this study was to investigate whether the Y-linked genes are associated with male fertility also in horses.

We have previously identified 34 genes and ESTs in the horse Y chromosome (ECAY). All genes were analyzed for expression profiles in 9 body tissues and evaluated for their copy numbers because human and mouse studies suggest that the most critical Y-linked male fertility genes are present in multiple copies and expressed only in testis. We identified 10 such genes in ECAY and used qRT-PCR to compare their expression in testes of 10 normal fertile stallions and 14 stallions with impaired fertility. Four ESTs and RBMY showed statistically significant differential expression between the two groups of stallions. Additionally, TSPY was highly upregulated in a stallion with severe sperm head morphological abnormalities. Studies are planned to investigate whether TSPY over-expression is caused by any structural or regulatory mutations in the coding region of equine TSPY. Quantitative RT-PCR allowed also evaluation of gene copy number and showed a decrease in average copy number of four different transcripts in stallions with compromised fertility. This study for the first time identifies potential candidate genes for male fertility in horses and demonstrates direct association of differential expression of ECAY genes with impaired fertility in stallions. The findings are expected to provide useful tools for fertility assessment in prospective breeding stallions.

Category: Graduate Student

Abstract 8 - Contributed Paper

Linkage mapping of the harlequin locus in the Great Dane.

K.L. Tsai[1], L.A. Clark[1], A.N. Starr[2], K.E. Murphy[2]
[1]Dept. of Veterinary Pathobiology, Texas A&M Univ., College Station, Texas, U.S.A.; [2]Dept. of Genetics and Biochemistry, Clemson Univ., Clemson, South Carolina, U.S.A.

The harlequin coat pattern of the Great Dane is a bigenic trait caused by the interaction of the merle allele of SILV and the harlequin locus, H. H is a dominant modifier of the merle coat pattern that results in patches of full pigment on a white background. In the homozygous state, H is embryonic lethal. A whole-genome screen using 280 microsatellite markers was carried out using several families of Great Danes and resulted in multiple significant LOD scores (maximum LOD = 4.07) on the telomeric end of chromosome 9. Subsequent haplotype analyses using these data defined a 1.3 Mb region containing the H locus. Genotyping of 27 SNPs and 3 INDELs in this region revealed a conserved haplotype in harlequin dogs. The haplotype spans 225 Kb and harbors 3 genes. None of these genes is known to have a role in pigmentation.

Classification: Postdoc

Abstract 9 - Contributed Paper

Loss of Function Mutations in Angiopoietin-like Proteins (ANGPTLs) Contribute to Plasma Triglyceride Levels.

W. Yin, S. Romeo, H.H. Hobbs, and J.C. Cohen.
McDermott Center for Human Growth and Development and the Howard Hughes Medical Institute at the University of Texas Southwestern Medical Center, Dallas, Texas

Angiopoietin-like proteins (ANGPTLs) constitute a family of seven secreted proteins that contain a coil-coil domain at the N terminus and a fibrinogen-like domain at the C terminus. Two family members, ANGPTL3 and ANGPTL4, inhibit lipoprotein lipase (LPL), resulting in increased in plasma triglyceride levels. We used population-based resequencing to characterize the phenotypic consequences of mutations in the genes encoding ANGPTL3, 4, 5, and 6. Rare nonsynonymous (NS) sequence variations in ANGPTL3, 4 and 5, but not 6, were significantly more common among individuals with plasma triglyceride in the lowest quartile compared to those in the highest quartile. To examine the effects of these sequence variations on the synthesis and function of ANGPTLs, we expressed the mutant proteins in HEK-293A cells. Of 23 missense alleles that were associated with low plasma triglyceride levels, 13 prevented secretion of the mutant proteins, while 8 others failed to inhibit LPL activity.
Taken together, our data indicate that ANGPTL3, ANGPTL4 and ANGPTL5 play similar but nonredundant roles in triglyceride metabolism. We hypothesize that these three ANGPTL proteins co-ordinate the partitioning of triglyceride-derived fatty acids among different tissue beds in response to metabolic needs.

Classification: Postdoc

Abstract 10 - Contributed Paper

The ER stress transcription factor XBP1s protects against Amyloid-beta neurotoxicity.

Yan Zhang, Sergio Casas-Tinto, Melisa Gomez-Velazquez, Marco Morales-Garza, Diego E. Rincon-Limas and **Error! Reference source not found.**.
Department of Neurology, University of Texas Medical Branch, Galveston, TEXAS, 77550

Alzheimer's disease (AD) is a devastating neurodegenerative brain disorder for which there is no cure. The most prominent pathologic hallmark in the AD brain is the abnormal accumulation of the amyloid beta42 (Aß) peptide, but the exact pathways mediating Aß neurotoxicity are virtually unknown. For instance, ER stress is activated in AD; however, mostly indirect evidence suggests that ER stress plays a role in Aß pathogenesis. We report that Aß activates the ER stress response factor *X-box binding protein 1* (*XBP1*) in transgenic flies and in human neuroblastoma, yielding its active form, the transcription factor XBP1s. Remarkably, XBP1s is neuroprotective in flies expressing Aß and in human neuroblastoma treated with Aß oligomers. We also demonstrate that XBP1s prevents the accumulation of free Calcium in the cytosol, thus explaining its protective activity. Together, these results highlight the functional relevance of XBP1s in the ER stress pathways triggered by AD, and uncover the potential of XBP1 as a therapeutic target for AD and other diseases characterized by ER stress.

Classification: Postdoc

Abstract 11 - Contributed Paper

Novel mitochondrial disease resulting from an ANT2 null human

Jaeckle Santos, L.J., Baker, L.A., Garg, V., and Zinn, A.R
University of Texas Southwestern Medical School at Dallas

We present the clinical and molecular analysis of a male patient with apparent mitochondrial disorder and a spectrum of congenital anomalies including cataracts, congenital kidney stones, developmental delay, sensorineural deafness and multiple mild heart defects. The patient has a family history of cataracts and calcium oxalate kidney stones, all appearing late in life. Array Comparative Genomic Hybridization revealed a 260kb deletion on Xq24 encompassing 4 genes and 1 hypothetical protein, including the mitochondrial Adenine Nucleotide Translocase, ANT2, which is responsible for ADP/ATP exchange and one of the most abundant mitochondrial proteins. Non-homologous X-linked genes exist as a single copy in males and the resulting deletion makes the patient a functional null. Fluorescence in situ hybridization confirmed the deletion to be carried by the patient's mother. Cataracts and kidney stones present in extended family members were found to be unlinked to the Xq24 deletion.

Given similar clinical characteristics and 2 deleted mitochondrial genes, we explored the possibility of our patient suffering from genetic mitochondrial disease. Consistent with mitochondrial dysfunction, mitochondrial membrane potential was consistently elevated and superoxide production increased nearly 3 fold over controls, despite no change in mitochondrial content. The mitochondrial DNA of the patient was found to harbor numerous deletions, likely the result of increased oxidative stress. Finally, the apoptotic index of cultured lymphoblasts was found to exceed 90%. Antioxidant therapy was able to partially rescue the high rate of apoptosis to that of control cell lines without antioxidants, and represents a viable treatment option. Mouse models of the 4 genes implicate mutations in the ANT2 gene as a possible cause of congenital heart defects in humans, as ANT2 null mice die embryonically from massive cardiac septal defects, similar to those seen in our proband, although this remains unconfirmed. Loss of ANT2 in our patient results in a novel mitochondrial disease with congenital structural anomalies, and may be involved in more common cardiac birth defects.

Classification: Graduate Student

Abstract 12 - Contributed Paper

Evolutionary Constraints and the gene expression pattern of Duplicated Genes of the Rhodobacter sphaeroides 2.4.1

Lin Lin*, Kristen Schroeder, Anne Peters, and Madhusudan Choudhary
Department of Biological Sciences, Sam Houston State University, Huntsville, Texas, U.S.A., 77341

Rhodobacter sphaeroides 2.4.1 belongs to α-3 subdivision of Proteobacteria. Unlike most prokaryotes, R. sphaeroides possesses a complex genome which consists of two circular chromosomes, chromosome I (CI, ~3.0 Mbp), chromosome II (CII, ~0.9 Mbp), and five endogenous plasmids; and its genome has been completely sequenced, assembled, and fully annotated. Along with other anoxygenic photosynthetic bacteria, R. sphaeroides 2.4.1 has provided a lot of physiological, biochemical, and biophysical information greatly contributing to our understanding of energy balance, physiological diversity and metabolic capabilities of these organisms. The complex genome and the abundance of gene duplication in R. sphaeroides provide an understanding to the evolution of the diverse metabolic functions as well as the evolution of complex prokaryotic genomes. A complete analysis of the R. sphaeroides genome revealed that approximately 34% of the total genes were duplicated in its genome. About 50% of gene duplications were found in two copies. These gene duplications were distributed on the different replicons and represented diverse metabolic functions of which a majority of them belongs to the COGs categories of metabolism and cellular processes. Thus, the mechanism of gene duplication for the evolution of gene functions is more prevalent for the genes that are involved in metabolism and cellular processes. Comparisons of synonymous and nonsynonymous nucleotide substitutions were also performed on each duplicated gene pair to compare the modes and the level of evolutionary constraints that these gene duplications experience. Of the randomly sampled 25 gene pairs from the R. sphaeroides genome, a majority of them (eighteen of duplicated gene pairs) showed that the rates of non-synonymous substitutions were significantly lower than the rates of synonymous substitutions in their coding sequences. Therefore, the majority of the gene duplications in the R. sphaeroides genome were under purifying selection as reflected in the ratio ranging from 0.089 to 0.70. In a preliminary investigation, forty duplicated gene pairs of R. sphaeroides were analyzed for their expression patterns. Out of 40, twelve pairs expressed at different levels, but both copies were expressed in all conditions. Another twelve gene pairs were differentially expressed, with one copy not being expressed in at least one growth condition. Sixteen pairs belong to another class where one copy in each pair remains silent under all growth conditions examined so far; it means that this copy may be pseudogene or no suitable growth condition is presently known for its expression. The future work will be extended to an analysis of the evolutionary constraint and gene expression patterns for all duplicated genes which have recently been identified in the genome of R. sphaeroides.

Category: Graduate Student

Abstract 13 - Contributed Paper

The mismatch repair heterodimer MutSβ, and the nucleotide excision repair protein complexes, XPA-RPA and XPC-RAD23B interact on DNA interstrand crosslinks.

Junhua Zhao[1], Aklank Jain[1], Ravi R. Iyer[2], Paul L. Modrich[2], and Karen M. Vasquez[1]*
[1]Department of Carcinogenesis, The University of Texas M. D. Anderson Cancer Center, Smithville, TEXAS 78957 and [2]Department of Biochemistry and Howard Hughes Medical Institute, Duke University Medical Center, Durham, NC 27710, U.S.A.

DNA interstrand crosslinks (ICLs) are among the most cytotoxic types of DNA damage, and thus ICL-inducing agents, such as psoralen, have been used clinically as chemotherapeutic drugs. Psoralen-modified triplex-forming oligonucleotides have been used to target ICLs to specific genomic sites in cells to increase the selectivity of these agents. However, how the TFO-directed psoralen ICLs (Tdp-ICLs) are recognized and processed in human cells is not clear. Previously, we reported that two essential nucleotide excision repair (NER) protein complexes, XPA-RPA and XPC-RAD23B, recognized ICLs in vitro, and that cells deficient in the DNA mismatch repair (MMR) complex MutSβ were sensitive to psoralen ICLs. To further investigate the role of MutSβ in ICL repair and the potential interaction between proteins from the MMR and NER pathways on these lesions, we performed electrophoresis mobility-shift assays, and chromatin immunoprecipitation analysis of MutSβ and NER proteins with Tdp-ICLs. We found that MutSβ bound to Tdp-ICLs with high affinity and specificity both in vitro and in vivo, and that MutSβ interacted with XPA-RPA or XPC-RAD23B in recognizing Tdp-ICLs in vitro. These data suggest that proteins from both the MMR and NER pathways interact in the recognition of ICLs. Our findings provide a mechanistic link by which proteins from multiple repair pathways contribute to ICL repair, which should assist in the development of improved ICL-based chemotherapeutic strategies.

Classification: Postdoc

Abstract 14 - Contributed Paper

Development of Novel Methods to Detoxify Sulfur Mustard Gas Using a Nucleophilic Agent

Stephen Boulware, Michael C. MacLeod, and Karen M. Vasquez
Department of Carcinogenesis, The University of Texas M.D. Anderson Cancer Center, Science Park-Research Division, 1808 Park Road 1C, Smithville, TEXAS 78957

Mustard gases are considered a class of chemical threat agents, and therefore it is important to develop methods to detoxify these agents in human cells. As a potent electrophile, mustard gas can damage nucleophilic sites (e.g. cellular proteins and nucleic acids), resulting in inflammation, cell death, mutagenesis, and/or carcinogenesis. Full sulfur mustards have two reactive chloro-ethyl groups and are known to form monoadducts and to a lesser extent, DNA interstrand crosslinks. Chloro-ethyl-methyl sulfide (CEMS) and chloro-ethyl-ethyl-sulfide (CEES) are the half mustards that can be used as model electrophiles to determine analogous conditions for full sulfur mustard exposure. However, CEMS and CEES form only monoadducts due to the presence of a single reactive group. Our research uses a nucleophilic substance, dithiopurine (DTP), as a scavenger to counter the effects of sulfur mustards as a preventative agent. DTP is an innocuous agent that elicits little to no toxic effects, but reacts facilely with CEMS and CEES. NTCT 2544 skin keratinocytes are used as a cellular model using a sodium hydroxide (CEMS) or phosphate (CEES) buffer system as vehicle for exposure to the half mustards and DTP. When cells were exposed to CEMS for 4 hours, the LD50 (determined by MTT assay) was determined to be 3.5 mM, but if 1.5 mM DTP was used as a scavenger, the LD50 increased to 5 mM. A blue-white mutation screen, using a supF mutation-reporter was used to determine mutagenesis by transfecting the shuttle vector psupFG1 into mammalian cells, and then screening for mutations that occurred in the mammalian cells through MBM7070 indicator E. coli. The mutation frequencies of increasing concentrations of CEMS to 0.8 mM produced only nominal background mutations. However, when the cells were exposed to 1.2 mM CEMS, there was a significant increase in mutation frequency at ~7-fold above the background levels. Strikingly, when 1.5 mM DTP was administered to the cells prior to treatment with CEMS (at 1.2 mM) no mutations were detected above the background levels. To confirm our data, we exposed the cells to 1.2 mM CEMS and increasing amounts of DTP. The result was a DTP dose-dependent reduction in the CEMS-induced mutations. Our results from studies with CEES and DTP were similar to those with CEMS. Randomly selected mutants from each treatment group were characterized by DNA sequencing. These results revealed that the majority of the CEMS or CEES-induced mutations were point mutations, and several mutants were the result of deletion or rearrangement events. It can be concluded that nucleophilic scavengers such as DTP can minimize the toxic effects of half mustards, and may provide a valuable tool in counteracting bioterrorism events using electrophilic mustard gases.

Classification: Technician

Abstract 15 - Contributed Paper

Cruciform-forming Inverted Repeats Mediated Microinversions that Distinguish the Human and Chimpanzee Genomes

Albino Bacolla[1], Jessica Kolb[2], Nadia A. Chuzhanova[3], Josef Högel[2], Karen M. Vasquez[1], David N. Cooper[4] and Hildegard Kehrer-Sawatzki[2]

[1] Department of Carcinogenesis, The University of Texas M.D. Anderson Cancer Center, Smithville, Texas 78957, U.S.A. [2.] Institute of Human Genetics, University of Ulm, Albert-Einstein-Allee 11, 89081 Ulm, Germany. [3.] School of Computing, Engineering and Physical Sciences, University of Central Lancashire, Preston PR1 2HE, UK. [4.] Institute of Medical Genetics, School of Medicine, Cardiff University, Cardiff CF14 4XN, UK

Submicroscopic inversions contribute to the genomic divergence between humans and chimpanzees. Those microinversions flanked by segmental duplications (SDs) of >1kb are presumed to result from non-allelic homologous recombination between SDs in inverted orientation. However, the mechanisms underlying inversions that are not flanked by large SDs are not well understood. We have investigated 35 such inversions, ranging in size from 51 to 22056-nt with a view to characterizing the sequences in the breakpoint-flanking regions. Using the macaque genome as an outgroup to determine the lineage specificity, we noted that the majority (N=31; 89%) of these inversions were associated with deletions (of between 1 and 6754-nt in length) immediately adjacent to one or both inversion breakpoints. Sequences containing partial retrotransposon elements belonging to either the Long Terminal Repeat (LTR) or non-LTR (L1) classes were found to be overrepresented within 500-nt of the inversion breakpoints, although in no case did they span the breakpoints on both sides in the ancestral (non-inverted) sequence. Overrepresentations of direct and inverted repeats, ≥6-nt in length and capable of non-B DNA structure formation, were noted in the vicinity of breakpoint junctions suggesting that these repeats could have contributed to double strand breakage and/or mutagenesis. Since cruciform-forming inverted repeats were a consistent feature of the inversion breakpoint flanking regions, we infer that these inversions are likely to have originated primarily through the resolution of Holliday junction-like cruciform structures. Sequences capable of non-B DNA structure formation have previously been implicated in promoting gross deletions and translocations causing human genetic disease. We conclude that non-B DNA forming sequences may also have promoted the occurrence of mutations in an evolutionary context, leading to gross genomic rearrangements including the various inversion/deletions that now distinguish the human and chimpanzee genomes.

Classification: Postdoc

Abstract 16 - Contributed Paper

Use of a Werner knockdown cell line to investigate the role of WRN in mammalian recombination.

Jennifer J. Rahn, Luis Della-Coletta, Megan Lowery, Tiffany Limanni, Gerry M. Adair, Rodney S. Nairn
UT MD Anderson Cancer Center, Science Park Research Division, Department of Carcinogenesis.

Werner syndrome in a rare autosomal recessive progeroid disease associated with advanced onset of aging characteristics like cataracts, greying of the hair, and diabetes as well as certain types of cancer. Werner syndrome patients have loss of function mutations in the Werner helicase gene (WRN), which encodes a member of the RecQ helicase family and has been shown to have important roles in a variety of pathways in the cell including DNA replication, DNA repair, and telomere maintenance. This protein interacts with a wide variety of proteins in all of these cellular processes indicating its central role in maintenance of genome stability. While all the functions of WRN in humans are not precisely understood, its potential yeast homologs Sgs1 and Srs2 have been shown to be involved in recombinational repair of double-strand breaks by suppressing crossovers and processing non-homologous ends. In order to investigate the potential role of WRN in mammalian cell mitotic homologous recombination, a stable shRNA WRN knockdown CHO cell line was established. A previously developed gene targeting assay system at the hemizygous APRT locus was employed using insertion-type vectors with long and short end-blocking 3'-OH nonhomologies. This assay examined the effects of WRN knockdown on recombination efficiency and the distribution of crossover vs. conversion recombinants. The WRN knockdown cell line exhibited reduced targeted and untargeted recombination rates when compared to the parental cell line. When the distribution of recombinant events was analyzed, the WRN deficient cell line was shown to have a very specific recombination phenotype in that no recombination events involving integration of a repaired targeting vector were recovered when long terminal nonhomologies were present in the targeting vector. This data suggests a potential role for WRN in stabilizing recombination intermediates formed when terminal nonhomologies are present. Supported by CA097175.

Category: Postdoc

Abstract 17 - Contributed Paper

A conditional mouse model for assessing BLM in homologous recombination

A.D. Brown[1] and A.J.R. Bishop[1,2]
[1]Department of Cellular and Structural Biology, [2]Greehey Children's Cancer Research Institute, The University of Texas Health Science Center at San Antonio, San Antonio, TEXAS, U.S.A., 78229.

Bloom's Syndrome (BS) is a rare, autosomal recessive disorder that results in an increased propensity of various cancers. The gene mutated in BS, BLM is one of a five-member family of RecQ helicases found in humans. In addition to cancer predisposition and early onset, clinical features of BS patients include dwarfing, facial abnormalities and fertility complications. Clinical diagnosis of BS is through identification of increased levels of sister chromatid exchange (SCE). Along with elevated SCE, cellular phenotypes of BS patient's cells include symmetric multiradial rearrangments and chromosomal breaks, of which results in chromosomal instability and cancer promotion. Although the exact function of BLM is still unresolved, the cellular phenotype of elevated SCE suggests a role in homologous recombination (HR) and DNA replication. *In vitro* experiments indicate that BLM activity is structure-specific, and that this action is anti-recombinogenic. Studies to define this role *in vivo* have had limited success due to BLM's requirement in mouse development. To begin to assess the role of BLM in HR *in vivo*, we have utilized a conditional BLM mouse model and the *in vivo* p^{un} eye-spot assay to detect HR. In addition to its anti-recombinogenic role, BLM also undergoes posttranslational modifications following various types of DNA damage. Particularly of interest is the phosphorylation of Thr99 and Thr122 by the gene product responsible for the disease ataxia telangiectasia (ATM) following ionizing radiation (IR) exposure. We will also use this model to understand the role of BLM in IR-induced HR repair. Our preliminary data confirms BLM involvement in HR. Mice deficient in BLM have an increased frequency of HR following endogenous DNA damage compared to wild-type. Additionally, mice heterozygous for BLM also have a moderate increase in HR frequency following endogenous DNA damage compared to wild-type mice, and this dosage affect is consistent with previous findings.

Classification: Graduate Student

Abstract 18 - Contributed Paper Read by Title only

DNA Structure-induced Genetic Instability.

Guliang Wang and Karen M. Vasquez*.
Department of Carcinogenesis, University of Texas MD Anderson Cancer Center, Science Park-Research Division, Smithville, Texas, U.S.A., 78957.

Naturally occurring DNA repeat sequences can form non-canonical DNA structures such as H-DNA and Z-DNA, which are abundant in mammalian genomes. Here we show that both H-DNA and Z-DNA structures are intrinsically mutagenic in mammalian cells. We found that the endogenous H-DNA-forming sequence in the human c-MYC promoter induced mutation frequencies ~20-fold over background, largely in the form of double-strand breaks (DSBs). In mammalian cells, Z-DNA-forming CG(14) repeats also lead to DSBs, resulting in deletions. We found that the non-B DNA-induced deletions were, in part, replication-independent, and were likely initiated by "repair processing" cleavages surrounding the non-B-DNA structures (Wang & Vasquez, *PNAS*, 2004; Wang et al., *PNAS*, 2006). We are performing studies to determine the role of repair enzymes in H-DNA and Z-DNA-induced genetic instability in mammalian cells. Our findings suggest that both H-DNA and Z-DNA, which have been reported to correlate with chromosomal breakpoints in human tumors, are sources of genetic instability, and demonstrate that naturally occurring DNA sequences are mutagenic in mammalian cells and may contribute to evolution and disease. We have constructed novel transgenic mutation-reporter mice containing the H-DNA sequence from the human c-MYC promoter, or a Z-DNA-forming sequence from the human BCL-2 gene, both of which map to chromosomal breakpoints in human cancers (Wang et al., *JNCI*, 2008). We have detected genetic instability induced by these DNA structures in ~20% of the offspring, suggesting that these structures are mutagenic in a chromosomal context in a living organism.

Category: By title only

Abstract 19 - Poster

Association of alpha-actinin 3 gene expression with bovine feed efficiency.

Robert N. Vaughn, Kelli J. Kochan, Tonya S. Amen, Colette A. Abbey, Clare A. Gill, James O. Sanders, Andy D. Herring, David K. Lunt, Jason E. Sawyer, Penny K. Riggs
Texas A&M University

Genes affecting economically important traits in beef cattle such as marbling and tenderness have long received attention for their obvious and immediate applications within the meat industry. However, numerous other traits that are more difficult to quantify but are no less important, such as feed efficiency and female productivity, have received considerably less attention so far. Genetic mechanisms influencing these traits remain poorly understood. One objective of the McGregor Genomics Project is to identify potentially valuable QTL for use in breeding programs for a variety of these traits. Approximately 180 F2 Nellore-Angus steers were assessed for feed efficiency as determined by computation of model predicted residual consumption (MPRC; Amen, 2007). Animals with the highest or lowest MPRC values were identified as "most efficient" or "least efficient." We extracted RNA from skeletal muscle from the 14 most efficient and 14 least efficient animals for microarray analysis. We used data generated from Agilent bovine oligo microarrays to identify candidate genes for further study. Among differentially expressed genes verified between the two groups, α-actinin 3 (*ACTN3*), was expressed nearly 3-fold higher in the inefficient group compared with the efficient group. *ACTN3* is expressed only in fast twitch muscle fibers. Actinins are myofilament proteins essential to z-line attachment for actin fibers, and have been shown to bind factors relating to myofiber differentiation as well as muscle contraction. This project was funded in part by America's beef and veal producers through the $1 per head check off and by Texas AgriLife Research.

Category: Graduate Student

Abstract 20 - Poster

Identification of differentially activated diet responsive gene networks in Low versus High LDL responder baboons. .Marshall Frazier[1]*, Jeremy P. Glenn[1], Shifra Birnbaum[1], John L. VandeBerg[1,2], Laura A Cox[1,2].
[1.]Department of Genetics, [2.] Southwest National Primate Center, Southwest Foundation for Biomedical Research, San Antonio, Texas

Background: Low Density Lipoprotien (LDL) transports cholesterol into cells and high levels of LDL-cholesterol (C) have been linked to heart disease and atherosclerosis.The goals of this study were to identify genes and networks of genes that 1) are central to the dietary response to fat and cholesterol and 2) differ between animals with a low LDL response compared with those with a high LDL response. Methods: Baboons discordant for LDL-C were selected and fed a high cholesterol, high-fat diet for 7 weeks. Liver biopsies were collected before and after the diet challenge. RNA extracted from the liver biopsies was used to interrogate gene arrays. Network analysis was performed on differentially expressed genes to identify genes that are central to the response to dietary fat and cholesterol. Quantitative RT-PCR was used to validate expression profiles of genes central to the respone. Results: AKT1 which is central to nutrient responsive signaling showed no change in the high responders when comparing the high-fat, high-cholesterol diet versus the chow diet. AKT1 showed a marginally significant increase in the livers of low LDL responders when comparing the high-fat, high-cholesterol diet versus the chow diet. Consistent with the gene array data, NFκB and HNF4α which also play roles in nutrient responsive signaling were not differentially expressed. Conclusion: Network analysis of gene expression data suggest that AKT1, HNF4α and NFκB are central to the LDL-C response to dietary fat and that the response differs between low and high LDL responders. Future Directions: Determine if protein expression (gene products) differs by diet for these central hub genes.

Classification: Undergraduate Student

Abstract 21 - Poster

Role of p24 Genes in Egg Laying and Developmental Behavior

Stephanie T. Grady, Julie R. Pate, and Ginger E. Carney
Department of Biology, Texas A&M University

Abstract: The organism Drosophila melanogaster has proven to be a respectable genetic model for analyzing behavior. Genes function within signaling pathways to regulate a variety of behavioral responses, such as ovulation and egg laying. Animals lacking some p24 genes do not lay eggs. p24s may be responsible for trafficking cargo vesicles from the endoplasmic reticulum to the Golgi apparatus of cells. Therefore, we hypothesize that p24 proteins traffic an ovulation or oviposition signal within a specialized set of cells. However, specificities of function and the location of expression of the p24 genes remain unidentified. Mutants in three genes of the p24 family (logjam, eclair, and baiser) do not lay eggs. To determine if other p24s are necessary for egg laying or development, we are reducing their expression using RNA interference driven by ubiquitously expressed Gal4 drivers. We are also co-immunostaining with cell type-specific markers to verify which cells express p24s. Co-staining of p24 proteins and peptidergic cell markers would bolster the hypothesis that p24s function in relaying the signal to secrete neuropeptides. If the trafficking of signals is blocked due to lack of p24 gene function, then neuropeptides controlling ovulation and egg laying would not be secreted, and eggs would not be oviposited as shown in some of the p24 RNAi deficient animals.

Category: Graduate Student

Abstract 22 - Poster

Fitting it all together: How courtship-responsive genes affect male reproductive behaviors.

Lisa L. Ellis and Ginger E. Carney. Department of Biology, Texas A&M University.

Behavior is a complex output regulated by genetics, nervous system function and environmental stimuli. We are interested in better understanding the interplay amongst these input pathways and their influence on behavior. To address this question, we are studying Drosophila melanogaster male courtship behavior.
We assayed gene expression changes in the nervous system due to courtship interactions via microarray analysis of Drosophila male head tissue. Comparing expression profiles between males that courted a female and males that were mock exposed identified 31 courtship-responsive genes. Our study identified a known sex-determination target, female-specific independent of transformer (fit) that is expressed in adipose tissue. Courtship behavior is regulated in part by the sex-determination pathway, though few targets of this pathway are known. It is likely that other candidate genes from our experiments are targets of this pathway.
We are utilizing RNAi and null alleles to determine fit's role in sex determination and reproduction as well as to understand how adipose tissue affects neural physiology and behavior. Analysis of candidate gene mutants reveals that egghead (egh) is required for robust male courtship activity. We are utilizing RNAi alleles to further understand egh's role in reproduction.

Category: Graduate Student

Abstract 23 - Poster

Linkage and Recombinational Characteristics of the X chromosome for the Gray Short-Tailed Opossum, *Monodelphis domestica.* Kory C Douglas[1], Anna Bennet[2], Chris Childers[2], and Paul Samollow[1.]
[1]Department of Veterinary Integrated Biosciences, College of Veterinary Medicine, Texas A & M University, College Station, TEXAS [2] Department of Biology, Georgetown University, Washington, D.C.

Availability of the first whole-genome sequence of a metatherian mammal, *Monodelphis domestica*, enables novel insights into the evolutionary histories and basic biology of mammals and other vertebrates. Because the metatherian-eutherian divergence pre-dates the human-mouse divergence (~ 75 million years ago) by roughly 100 million years, comparing the genomic structures and functional characteristics of these lineages provides unique opportunities for inferring evolutionary trends among genes and other conserved elements among mammalian lineages. The published opossum linkage map consists of 150 genetic markers covering the 8 autosomes. The map reveals that opossum has the lowest recombination rate known among mammals and a lower recombination rate in females than in males, which differs from observed patterns in other vertebrates with extensive linkage mapping data (except sheep). Based on differences in sequence characteristics, such as higher G+C and CpG dinucleotide content, it has been postulated that the average recombination rate on the opossum X chromosome should be much higher than that on the autosomes. However, data regarding recombinational characteristics of the opossum X chromosome have been lacking. We have developed 30 novel microsatellite markers spanning most of the 76 Mb opossum X chromosome and genotyped 571 individuals representing 35 three-generation families. We report here the results of our analyses of linkage and recombination among these markers and interpret our findings with regard to the recent theories regarding the relationship between recombination rate, biased gene conversion, and the G+C contents of chromosomes and sub-chromosomal regions. We also highlight the discrepancies between our X-chromosome linkage map and the most recently released X chromosome assembly from MonDom5, the most current genome assembly.

Classification: Graduate Student

Abstract 24 - Poster

Efficient UvrABC Processing of TFO-directed Psoralen-DNA Interstrand Crosslinks

Laura A. Christensen and Karen M. Vasquez.
Department of Carcinogenesis, Science Park-Research Division, University of Texas M.D. Anderson Cancer Center, Smithville, Texas, U.S.A., 78957.

Abstract:
Photoreactive psoralens have been used extensively in the treatment of skin disorders such as psoriasis. These compounds can form DNA interstrand crosslinks (ICLs) preferentially at 5'-TpA-3' sites in double-stranded DNA. In eubacteria, the multi-subunit endonuclease UvrABC plays a key role in repairing psoralen ICLs, hydrolyzing the 9th phosphodiester bond to the 5' side and the 3rd phosphodiester bond to the 3' side of a psoralen ICL. Psoralen-modified triplex-forming oligonucleotides (TFOs) can be used to target psoralen ICLs to specific sites in duplex DNA, which may be used to therapeutic advantage. Previous studies of pyrimidine-rich methoxypsoralen-modified TFOs have indicated that the presence of the TFO inhibits cleavage by UvrABC by as much as 80% compared to ICL alone, presumably due to the TFO blocking the endonuclease cleavage site in the underlying duplex target substrate. As different binding and crosslinking chemistries may alter the processing of TFO-directed ICLs, here we investigated the effect of purine-rich TFOs on the processing of 4'-(hydroxymethyl)-4,5',8-trimethylpsoralen (HMT) ICLs by the purified UvrABC protein complex. Our studies with an HMT-modified purine-rich TFO indicate that UvrABC cleaves the purine strand of the duplex DNA ~3 bases on the 3' side and ~9 bases on the 5' side of the ICL, within the TFO binding region, consistent with published work employing a pyrimidine-rich psoralen-modified TFO. In contrast, UvrABC nuclease cleaved the purine-rich psoralen-TFO ICL more efficiently than ICL alone. Further, binding studies showed that the TFO dissociated from its duplex binding site in the presence of UvrA and UvrB. Our results suggest that UvrABC can process psoralen-ICLs in the presence of a TFO, supporting the use of triplex technology as a useful method to induce site-specific DNA damage to facilitate genome modification.

Classification: Technician

Abstract 25 - Poster

Evaluation of a Novel FMR1 PCR Assay that Can Amplify Fragile X Full Mutations.

Stela Filipovic-Sadic[1], Gary J Latham[1], Sachin Sah[1], Liangjing Chen[1], Edward Sekinger[1], Julie Krosting[1], Tiffany Sanford[1], Elizabeth Mambo[1], Timothy Stenzel[1], Stephen Brown[2], Andrew Hadd[1].
[1]Asuragen, Inc., Austin, TEXAS, United States, [2]University of Vermont College of Medicine, Burlington, VT, United States.

Background: Fragile X is a trinucleotide repeat disease caused predominantly by the expansion of CGG sequences in the 5' untranslated region of the FMR1 gene. Patients with full mutations (>200 CGG repeats) often present classic Fragile X syndrome, whereas individuals with the FMR1 premutation (55-200 CGG repeats) are at risk for Fragile X-associated tremor ataxia syndrome (FXTAS) or primary ovarian insufficiency (FXPOI). Fragile X diagnostic testing typically relies on two tests, PCR and Southern Blotting. FMR1 PCR is limited to amplification of only 100-200 CGG repeats, and cannot differentiate female homozygous samples and heterozygous samples containing one unamplifiable allele. As a result, many, if not all, samples evaluated in clinical laboratories are reflexed to the Southern blot, which severely constrains the workflow and limits routine testing. The purpose of this study was to evaluate a novel PCR technology to accurately detect full mutation alleles, resolve female zygosity, and provide a comparison with results from Southern Blotting.
Methods: Human genomic DNA (gDNA) samples comprising 20 to 940 repeats were obtained from the Coriell Institute for Medical Research, Sigma-Aldrich, and a clinical collaborator. An Asuragen laboratory developed test (LDT) including FMR1 primers and a GC-rich PCR buffer was used to amplify all samples in an ABI 9700 thermocycler. Amplicons were sized by agarose gel electrophoresis and/or capillary electrophoresis (CE) on an ABI 3130xl instrument.
Results: The Asuragen LDT successfully and reproducibly amplified gDNA bearing repeat numbers that spanned the full range of Fragile X disease thresholds, from 20 to at least 940 repeats. The assay successfully amplified a "mock" full mutation mosaic sample comprised of 2 ng 940 CGG repeat allele in a background of 38 ng 23 CGG repeat (i.e., 5% 940 CGG/95% 23 CGG). Reproducibility testing demonstrated concordant results with normal, premutation, and full mutation samples across three separate operators on three different days. An additional PCR innovation enabled differentiation of female heterozygous and homozygous alleles. Finally, preliminary PCR evaluations of clinical specimens accurately sized full mutation alleles, and indicated greater sensitivity in the detection of several full mutations compared to Southern Blotting, including a sample from a patient with Fragile X clinical features where Southern blot had detected a pre-mutation but failed to detect mosaicism for a full mutation.
Discussion: Asuragen's LDT for Fragile X testing was demonstrated to amplify at least 940 CGG repeats, even in the presence of a nearly 20-fold excess of a much more readily amplified 23 repeat allele. The assay was reproducible across the range of clinically-relevant disease thresholds, and could be adapted to resolve female zygosity issues that drive sample reflexing to Southern blot. Consequently, the ability of the Asuragen PCR LDT to detect even very large full mutations and definitively interpret female homozygous samples suggests the possibility of a PCR-only workflow for routine Fragile X testing with superior sensitivity for mosaicism detection compared to Southern Blotting. The Fragile X PCR assay described here is planned for launch as a diagnostic service through Asuragen's CLIA laboratory.

Classification: Technician

Abstract 26 - Poster

microRNA Profiling of Renal Cell Carcinoma.

D.K. Garcia[1], D. Troyer[1], D. Parekh[1], I.M. Thompson[1], W. Grizzle[2], and S.L. Naylor[1].
[1]University of Texas Health Science Center at San Antonio and the [2]University of Alabama at Birmingham.

Abstract: MicroRNAs (miRNA) have recently been implicated as key molecules in the development of cancer. miRNAs regulate the expression of other genes at the level of transcription or translation and one miRNA can regulate many genes. miRNA expression will influence kidney cancer; however, only a limited amount of information has been gathered to date. To determine the expression profile of miRNA in kidney, we isolated RNA from pairs of normal and renal cell carcinoma (50 pairs from the Cooperative Human Tissue Network and 16 from the University of Texas Health Science Center at San Antonio). 27 pairs of tissue with RIN >7 (RNA Integrity Numbers) were sent to Asuragen for assay on two independent sets of Affymetrix DiscovArray chips. This chip has both known miRNAs and predicted ones. Analysis of the data indicated that of the >13,000 probes examined only a limited number of miRNAs are different comparing normal and tumor tissue. In contrast, the normal tissues were fairly homogeneous in expression. Using the parameters of markers with a >2 fold change with a probability of <0.05, six known microRNAs were found to be under expressed in tumors as well as three predicted miRNAs. Using the same parameters, 6 miRNAs were found to have much higher expression in tumors with an additional 15 predicted miRNAs that had significantly higher expression. To validate these data, we examined all 66 tumor/normal pairs and an additional 4 tumors by real time reverse transcriptase PCR for a subset of the miRNAs. >90% of the clear cell carcinomas over expressed miR-885-5p and under expressed miR-200c, miR-141, miR-187 and miR-138. Approximately 75% of the tumors over expressed miR-122a and miR-34b although these were not overlapping subsets of the tumors. Our data confirm Nakada et al [(2008) J.Path 216:418] for 5 miRNAs and indicate additional markers that comprise a distinct set of miRNAs that are changed in renal cell carcinoma. Experiments are underway to identify the pathways controlled by these microRNAs. (Supported by NCI grant U01 CA86402).

Classification: Technician

Abstract 27 - Poster

Preliminary Characterization of a Novel Equine Gene Potentially Associated with Spermatogenesis .

J. E. Shields[1], K. J. Kochan[1], J. Jeong[1], C. A. Abbey[1], T. Raudsepp[2], and P. K. Riggs[1,2].
Departments of [1]Animal Science and [2]Veterinary Integrative Biosciences, Texas A&M University, College Station, TEXAS, U.S.A.

We recently identified a gene (*NMES1*) that is expressed more abundantly in testis than any other tissue examined. Initial results suggested *NMES1* may play a role in cellular differentiation. We sequenced and carried out preliminary characterization of this novel gene in the horse to investigate its function and potential role in stallion spermatogenesis. Our initial BLAT search for the *NMES1* gene in the equine genome identified only a region that appeared to be orthologous to the third exon of the human, mouse, and bovine sequences. We designed PCR primers to amplify the conserved equine sequence and screened an equine CHORI-241 BAC library. After locating a BAC containing the gene, direct sequencing was performed by primer-walking along the BAC. This strategy yielded the full length genomic DNA sequence of *NMES1*. We identified several sequence variations (SNP) between the genomic sequence in the UCSC database and our BAC genomic DNA. The putative amino acid sequence for equine *NMES1* is 83 amino acids long. We also conducted fluorescence in situ hybridization and radiation hybrid mapping and localized *NMES1* to ECA 1q23.

Classification: Graduate Student

36th Annual Meeting of the Texas Genetics Society, Austin, TEXAS, April 2-4,2009

Presenters' Contact Information

Last Name	*First Name*	*E-mail*
Bacolla	Albino	abacolla@mdanderson.org
Boulware	Stephen	sboulwar@mdanderson.org
Brinkmeyer-Langford	Candice	cbrinkmeyer@cvm.tamu.edu
Brown	Adam	browna4@uthscsa.edu
Busch	Catherine	cbusch@cvm.tamu.edu
Butler	Jamie	jlb6736@tamu.edu
Christensen	Laura	lchriste@mdanderson.org
Douglas	Kory	kodouglas@tamu.edu
Ellis	Lisa	lellis@tamu.edu
Filipovic-Sadic	Stela	sfsadic@asuragen.com
Frazier	Marshall	Marshall_Frazier@yahoo.com
Fritz	Krista	kfritz@cvm.tamu.edu
Garcia	Dawn	GarciaD1@uthscsa.edu
Grady	Stephanie	stephaniegrady@tamu.edu
Jaeckle Santos	Lane	lane.jaeckle@utsouthwestern.edu
Lin	Lin	lxl005@shsu.edu
Morales Garza	Marco Antonio	mamoral1@utmb.edu, marconou1@gmail.com.
Paria	Nandina	naparia@cvm.tamu.edu
Rahn	Jennifer	jrahn@mdanderson.org
Shields	Jordan	jshields23@tamu.edu
Tessanne	Kimberly	ktessanne@cvm.tamu.edu
Tsai	Kate	ktsai@cvm.tamu.edu
Vaughn	Robert	bobv527@gmail.com
Zhang	Yan	yazhang@utmb.edu
Zhao	Junhua	junhuaz@mdanderson.org
Yin	Wu	wu.yin@utsouthwestern.edu
Vasquez	Karen	kvasquez@mdanderson.org

Previous Texas Genetics Society Meetings, 1974-2008

No.	Year	Location	Organizer		
1	1974	Galveston	Barbara Bowman		
2	1975	Houston	Margery Shaw, Tom Caskey		
3	1976	Austin	Eldon Sutton		
4	1977	San Antonio	John Prince		
5	1978	Dallas	Raymond Lewandowski		
6	1979	Galveston	Lillian Lockhart		
			President	**TGS Distinguished Geneticist Award**	**TGS Service Award**
7	1980	Houston	Eldon Sutton	--	--
8	1981	College Station	Barbara Bowman	--	--
9	1982	San Antonio	Robert Ferrell	C.P. Oliver	--
10	1983	Austin	Bob Sanders	Meta S. Brown	--
11	1984	Dallas	Lillian Lockhart	Bob Wagner	--
12	1985	Galveston	Arthur Beaudet	Rose Schneider	--
13	1986	Houston	Margery Shaw	T.C. Hsu	--
14	1987	College Station	Don Barnett	Margery Shaw	--
15	1988	Denton	Satish Srivastava	Eldon Sutton	--
16	1989	San Antonio	Frank Greenberg	Lillian Lockhart	--
17	1990	Austin	James Womack	Barbara Bowman	--
18	1991	Dallas	Charleen Moore	Dorethea Bennett	--
19	1992	College Station	Stephen Daiger	Bill Stone	--
20	1993	Galveston	Olivia White	Mike Siciliano	
21	1994	Houston	John VandeBerg	Jack Schull	--
22	1995	San Antonio	Mary Jo Harrod	Frank Greenberg	--
23	1996	Austin	Fred Elder	James Womack	--
24	1997	Dallas	Bill Stone	Louise Strong	Don Barnett
25	1998	Austin	Sue Naylor	Tom Caskey	Eldon Sutton
26	1999	Austin	Ann Killary	Arthur Beaudet	Olivia White
27	2000	Houston	Mike Siciliano	Robert Ferrell	Fred Elder
28	2001	San Antonio	Paul Samollow	Sue Naylor	Charleen Moore
29	2002	South Padre	Ronald Walter	Alfred Knudson, Jr.	Andrew Dewees
30	2003	Austin	Jim Derr	Masatoshi Nei	Sue Ann Berend
31	2004	South Padre	Robert Baker	James Lupski	Sue Naylor
32	2005	Dallas	Christi Walter	Robert Baker	Paul Samollow
33	2006	Galveston	Rodney Nairn	Bert O'Malley	James Womack
34	2007	San Antonio	Sue Ann Berend	Jacqueline Hecht	Robert Baker
35	2008	College Station	Carol Wise	Larry Thompson	Christi Walters
36	2009	Austin	Laura Cox	Richard Gibbs	TBA