

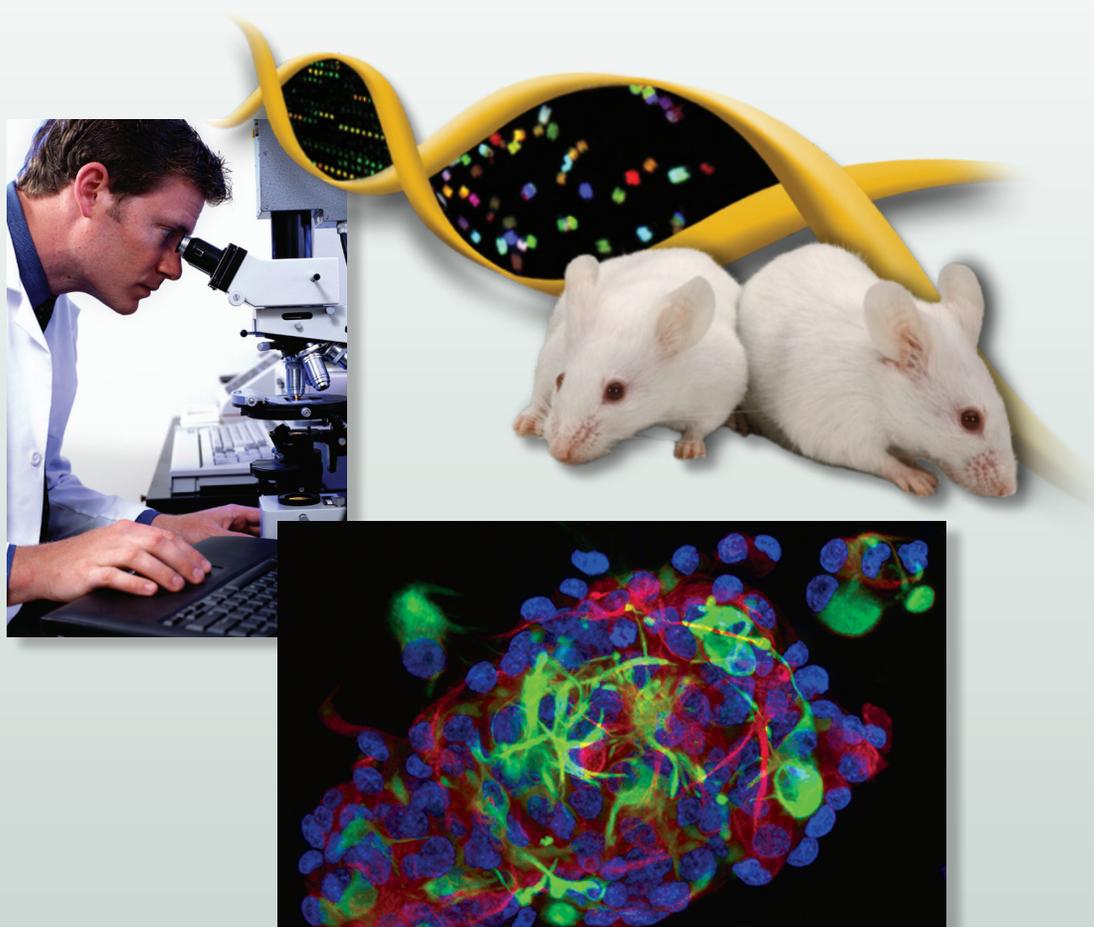


The National Institutes of Health

# NIH Comparative Biomedical Scientists Training Program Symposium

September 8–10, 2010

Natcher Conference Center, National Institutes of Health  
Bethesda, Maryland



**Molecular Pathology Unit  
Laboratory of Cancer Biology  
and Genetics  
Bldg. 37, Room 2000  
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Bethesda, MD 20892  
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## September 8, 2010

Welcome invitees, to this scientific symposium and training retreat, being held in the NIH Natcher Conference Center September 8-10, 2010, honoring the partnership established for interdisciplinary training of veterinarians in comparative pathology and biomedical research. Welcome to Michigan State University, North Carolina State University, University of Maryland, University of Illinois, and Purdue University from your hosts, The Intramural Research Divisions of The National Cancer Institute, The National Institute of Diabetes and Digestive and Kidney Diseases, The National Institute of Allergy and Infectious Diseases, The National Heart, Lung and Blood Institute, and The National Institute of Neurological Disorders and Stroke. As we commence this symposium, the training consortium is robust with scientifically and academically diverse institutional partners. Each member of the partnership contributes significantly to our mission.

The format of the symposium will be expanded from the 1<sup>st</sup> symposium held October 2-3, 2008. The scientific sessions, including presentations by outstanding investigators from our partnership universities and by NIH principal investigators, will be supplemented by additional presenters.

This year we anticipate graduating 6 veterinarians who have successfully achieved training as veterinary pathologists and who plan to defend their Doctor of Philosophy dissertations this Fall. Presentations of their original scholarship in research will be provided by imminent graduates including: Drs. Schantel Hayes and Yava Jones, of Michigan State University, Tanasa Osborne, of the University of Illinois, Kevin Woolard, of North Carolina State University, and Heather Shive and Philip Martin, of the University of Maryland.

Our objectives in this second symposium include 1) highlighting research and research training being accomplished by veterinarians training in the NIH GPP interdisciplinary DVM/PhD training program, 2) informing our veterinary college-GPP university partners about NIH research, and for 3) developing interactive collaborations among partnership university faculty and NIH investigators. Toward this end, our six anticipated program graduates will present their dissertation projects during scientific sessions on Thursday and Friday. We will have 4 poster sessions for our veterinary pathologists-in-training and invited veterinary students.

We appreciate the participation by our NIH and university invited speakers in this year's symposium. Once again partnership university research deans have nominated a faculty member from their institution to contribute a scientific talk on their research. Naturally a broad range of topics results, particularly as we include presentations from NIH investigators, chosen for their scientific interests and enthusiastic support for integrating knowledge on the biology of diseases affecting human beings and animals.

Our featured presentation will be delivered by Michael Lenardo, M.D. of the National Institute of Allergy and Infectious Diseases, Laboratory of Immunology. Dr. Lenardo directs another NIH Graduate Partnership training program known as the NIH Oxford Cambridge Scholars Program. He will highlight benefits being derived as the NIH becomes a community for partnership graduate training, in his talk entitled "International Collaboration Elucidates Severe Acute Respiratory Syndrome (SARS) Pathogenesis".

This year, we will also include a September the 8<sup>th</sup> pre-meeting workshop on the Biology of Animal Models of Human Diseases that will focus on nonhuman primate biology and pathology. The afternoon of Friday September 10 will feature a career planning/development session. A program directors meeting will be held on Thursday morning, September 9th.

Also new this year, through a competitive essay contest, we have provided 9 veterinary students with travel awards to allow them to participate in the symposium and present their current work as a poster presentation. These invitees from across the U.S., are listed in our meeting proceedings booklet.

Thank you for participating in our training program symposium.

R. Mark Simpson

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# **Acknowledgements**



## **Acknowledgements**

I would like to acknowledge and thank all the participants and sponsors of this symposium and the training program. Most noteworthy are those in-training, the NIH and university faculty investigators serving as mentors and graduate committee members, and the NIH staff members whose daily contributions make the program the valuable success it is. Many of these individuals are listed in the symposium participants list.

The program's success and continuing advancement follows enthusiastic support from our partners and NIH scientific leadership. Faculty from each university not only help to recruit, train, and mentor the trainees with proven curricular content developed over long personal tenures, but they also provide vision to the pathologists-in-training, for the unique benefits of this kind of novel interdisciplinary training. We are gratefully thankful for the support of faculty and administration at Michigan State University, North Carolina State University, University of Maryland, University of Illinois and Purdue University for accomplishing the partnership agenda.

In addition to our partnership university faculty, we benefit from invaluable educational contributions of our scientific staff members in the Molecular Pathology Unit, Laboratory of Cancer Biology and Genetics, Center for Cancer Research. My colleagues including Shelley B. Hoover, Jennifer B. Edwards, Bih-Rong Wei, Joshua D. Webster and John Hickerson are instrumental in operating the program and in providing training content to trainees. Holding this symposium is in large part due to the collective efforts of this outstanding group.

As we continue to strive to add value to the public health research agenda in the United States, I am indebted to the sustained backing from two critical NIH sources of support. I thankfully acknowledge those institute Scientific Directors with whom I have the pleasure of working. These include Robert Wiltout, Ph.D., NCI, Kathy Zoon, Ph.D., NIAID, Robert Balaban, Ph.D., NHLBI, Alan Koretsky, Ph.D., NINDS, and Ira Levin, Ph.D., NIDDK. Their leadership motivates me to continue the excellence brought about by the many others contributing and participating in the program. I am extremely grateful for the ongoing supportive collegial direction and advisement from our Director of the Center for Cancer Training, Jonathan S. Wiest, Ph.D. Finally, I appreciatively acknowledge the support and encouragement of my mentor and lab chiefs Glenn Merlino, Ph.D. and Stuart Yuspa, M.D. We acknowledge the generous support of the Aperio Technologies, Inc for their sponsorship of the Thursday noon meeting.

*R. Mark Simpson*



**The Molecular Pathology  
Graduate Partnership  
Program Consortium Members**



## The Molecular Pathology Graduate Partnership Program Consortium Members





# **NIH CBSTP Symposium Agenda**



The NCI Molecular Pathology Graduate Partnership Program in collaboration with  
NIAID, NIDDK, NHLBI, and NINDS announces the 2<sup>nd</sup>

## **NIH Comparative Biomedical Scientist Training Program (CBSTP) Scientific Symposium and Retreat**

September 8–10, 2010

The NIH Natcher Conference Center, Building 45, Room E1/E2, Bethesda, MD

### ***Four Parts of the Symposium***

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#### ***Part 1:***

**Pre-Meeting Workshop:  
Biology of Animal Models of Human Disease**  
Wednesday, September 8

#### ***Part 2:***

**Business Session**  
Thursday, September 9

#### ***Part 3:***

**CBSTP Symposium:  
Platform and Poster Presentations**  
Thursday and Friday, September 9–10

#### ***Part 4:***

**Career Session**  
Friday, September 10



The NCI Molecular Pathology Graduate Partnership Program in collaboration with  
NIAID, NIDDK, NHLBI, and NINDS announces the 2<sup>nd</sup>

## NIH Comparative Biomedical Scientist Training Program (CBSTP) Scientific Symposium and Retreat

September 8–10, 2010

The NIH Natcher Conference Center, Building 45, Room E1/E2, Bethesda, MD

### Wednesday, September 8

### Pre-Meeting Workshop

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|---------------------|--|
| 11:00 am – 12:50 pm | <b>Meeting Registration</b><br>(Veterinary students hang posters – Room C1/C2)<br><br><b>Session on:</b><br><i>Biology of Animal Models of Human Disease: Research on Non-Human Primates</i> |
| 12:50 pm            | <b>Opening Remarks/ Welcome</b><br>R. Mark Simpson, D.V.M., Ph.D.  |
| 1:00 pm – 1:45 pm   | <b>Jeremy Smedley, D.V.M.</b> , Animal Program Director, Laboratory Animal Sciences Program, National Cancer Institute<br><i>Biology and care of non-human primates</i>                      |
| 1:45 pm – 2:30 pm   | <b>J. Mark Cline, D.V.M., Ph.D.</b> , Professor of Pathology, Wake Forest University Medical Center<br><i>Nonhuman primate pathology</i>   |
| 2:30 pm – 2:45 pm   | <b>Break</b>   |
| 2:45 pm – 4:00 pm   | <b>J. Mark Cline, D.V.M., Ph.D.</b> , Wake Forest University Medical Center<br><i>Nonhuman primate models of disease</i>   |
| 4:00 pm – 4:15 pm   | <b>Break</b>   |
| 4:15 pm – 5:00 pm   | <b>Wednesday Evening Poster Session</b><br>CBSTP Travel Award Recipients   |
| 5:15 pm – 6:15 pm   | <b>CBSTP Trainee Meeting</b> (Room E1/E2)  |

### Thursday, September 9

### Business Session

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- |                   |   |
|-------------------|---|
| 7:00 am – 8:15 am | <b>NIH Partnership Training Program Directors Pre-Meeting Program Status Update and Discussion</b><br>(Breakfast – Bethesda North Marriott) |
| 8:15 am – 8:50 am | <b>Transition between Meetings</b><br>(Transportation provided)   |

- 7:45 am – 10:30 am     **Registration**  
(Hang all posters – Natcher Conference Center, Room F1/F2)
- 8:50 am – 8:55 am     **Opening Remarks / Welcome**  
R. Mark Simpson, D.V.M., Ph.D.
- 8:55 am – 9:45 am     **Featured Presentation:**  
*International collaboration elucidates Severe Acute Respiratory Syndrome pathogenesis*  
  
**Michael Lenardo, M.D.**, Senior Investigator, Laboratory of Immunology; Director, NIH Oxford-Cambridge Scholars Graduate Partnership Program, National Institute of Allergy and Infectious Diseases
- 9:45 am – 10:25 am     **Heather Shive, D.V.M.**, CBSTP fellow, Experimental Transplantation and Immunology Branch, National Cancer Institute  
*University of Maryland dissertation: Modeling germline Brca2 mutations in zebrafish*
- 10:25 am – 10:40 am     **Break**
- 10:40 am – 11:10 am     **Utpal Pal, Ph.D.**, Assistant Professor, University of Maryland  
*Interfering with transmission of Lyme disease pathogen from the vector to hosts*
- 11:10 am – 11:40 am     **Vanessa Hirsch, D.V.M., D.Sc.**, Senior Investigator, Viral Pathogenesis and Vaccine Section, National Institute of Allergy and Infectious Diseases  
*Lessons from Monkey Models for AIDS*
- 11:40 am – 12:20 pm     **Philip Martin, M.S., D.V.M.**, Cell and Cancer Biology Branch, National Cancer Institute  
*University of Maryland dissertation: Investigating the molecular mechanisms of androgen independent growth, metastasis, and EMT in a mouse model of prostate cancer*
- 12:20 pm – 1:35 pm     **Lunch**  
Sponsorship from Aperio Technologies, Inc.
- 12:40 pm – 1:05 pm     **Lunch Speaker:**  
**Joshua Webster, D.V.M., Ph.D.**, Staff Investigative Pathologist, Laboratory of Cancer Biology and Genetics, National Cancer Institute  
*Quantitative pathology using Aperio image analysis toolbox*
- 1:05 pm – 1:35 pm     **All Poster Session** – Thursday afternoon  
(Natcher Conference Center, Room F1/F2)
- 1:35 pm – 2:05 pm     **Sidonie N. Lavergne, D.V.M., Ph.D.**, Assistant Professor of Veterinary Biosciences, University of Illinois  
*Drug allergy, when pharmacology meets immunology*
- 2:05 pm – 2:35 pm     **Matthew Breen, Ph.D.**, Professor of Genomics, Department Molecular Biomedical Sciences, North Carolina State University  
*The Domestic Dog – A Genome with Two Tales*

- 2:35 pm – 3:15 pm **Kevin Woolard, D.V.M.**, CBSTP fellow, Neuro-Oncology Branch, National Cancer Institute  
*North Carolina State University dissertation: Comparative genomics of canine and human glioma stem cells: The dog faithfully recapitulates genomic alterations driving human glioblastoma*
- 3:15 pm – 3:35 pm **Break**
- 3:35 pm – 4:05 pm **Bibiana (Bibi) Bielekova, M.D.**, Investigator, Neuroimmunological Diseases Unit, National Institute of Neurological Disorders and Stroke  
*Unexpected mechanism of action of CD25 blocking Ab (daclizumab) in Multiple Sclerosis*
- 4:05 pm – 4:45 pm **Schantel Hayes, D.V.M.**, CBSTP fellow, Genetics of Development and Disease Branch, National Institute of Diabetes and Digestive and Kidney Diseases  
*Michigan State University dissertation: Identification and characterization of novel regulators of adipogenesis*
- 4:45 pm – 5:30 pm **All Poster Session** (Natcher Conference Center, Room F1/F2)

## Friday, September 10

## General Meeting

- 8:00 am – 8:10 am **Session Introduction**  
Mark Simpson, D.V.M., Ph.D.
- 8:10 am – 8:50 am **Tanasa Osborne, D.V.M.**, CBSTP fellow, Pediatric Oncology Branch and the Laboratory of Cancer Biology and Genetics, National Cancer Institute  
*University of Illinois dissertation: Role of elf4E in osteosarcoma metastasis*
- 8:50 am – 9:20 am **Alison Bauer, Ph.D.**, Associate Professor, Michigan State University  
*The role of toll-like receptor 4 and downstream pathways in ozone-induced lung inflammation and injury*
- 9:20 am – 10:00 am **Yava Jones, D.V.M.**, CBSTP fellow, Laboratory of Experimental Immunology, National Cancer Institute, Frederick  
*Michigan State University dissertation: The role of tumor necrosis factor (TNF) in acute colitis and colitis-associated colon cancer*
- 10:00 am – 10:20 am **Break**
- 10:20 am – 10:50 am **Kanta Subbarao, M.D., M.P.H.**, Senior Investigator, Emerging Respiratory Viruses Section, National Institute of Allergy and Infectious Diseases  
*Use of Animal Models in Influenza Vaccine Research*
- 10:50 am – 11:20 am **Suresh Mittal, D.V.M., Ph.D.**, Professor of Molecular Virology, Purdue University  
*Recombinant adenoviruses for development of vaccines against influenza*

- 11:20 am – 11:25 am **Career Session Introduction**
- 11:25 am – 11:55 am **Jonathan S. Wiest, Ph.D.**, Director, Center for Cancer Training, Laboratory of Cancer Biology and Genetics  
*NCI funding mechanisms for early stage investigators*
- 11:55 am – 1:00 pm **Lunch** (on your own)  
plus **All Poster Session** (Natcher Conference Center, Room F1/F2)
- 1:00 pm – 1:30 pm **Cynthia Dunbar, M.D.**, Senior Investigator, Hematology Branch, National Heart, Lung, and Blood Institute  
*Publishing in the scientific journal without perishing*
- 1:30 pm – 2:00 pm **Chand Khanna, D.V.M., Ph.D.**, Head, Tumor and Metastasis Biology Section, Pediatric Oncology Branch, National Cancer Institute  
*The Valued and Informed Perspective of a Comparative Scientist*
- 2:00 pm – 2:30 pm **Mark Hoenerhoff, D.V.M., Ph.D.**, Staff Scientist, Cellular and Molecular Pathology Branch, National Institute of Environmental Health Sciences  
*Forging successful collaborations as a peer*
- 2:30 pm – 2:50 pm **Break**
- 2:50 pm – 3:20 pm **David Caudell, D.V.M., Ph.D.**, Assistant Professor, Virginia Tech University  
*Navigating the Path to Academia: Resources, Funding, and Tenure*
- 3:20 pm – 3:50 pm **Barbara Davis, V.M.D., Ph.D.**, Professor, Tufts University  
*Investigative pathology and transitioning government, industry and academia*
- 3:50 pm – 4:20 pm **Susan Ewart, D.V.M., Ph.D.**, Associate Dean of Research and Graduate Studies and Professor, Michigan State University  
*Getting a start in an academic career*
- 4:20 pm – 4:25 pm **Summation**

**Biographies and Research Abstracts**  
**(Trainees with Dissertation Projects)**





### **A. Sally Davis, D.V.M**

Dr. Davis is currently a graduate scholar in the NCI Molecular Pathology GPP program in partnership with North Carolina State University and the National Institute of Allergy and Infectious Diseases, 2007-present.

She conducts her PhD research in the laboratory of Dr. Jeffery K. Taubenberger, M.D., Respiratory Virus Pathogenesis and Evolution Section, Laboratory of Infectious Diseases, NIAID. Dr. Davis received her D.V.M. and Residency Certificate in Veterinary Anatomic Pathology in 2007 and 2009, respectively from North Carolina State University College of Veterinary Medicine. She also has a BA in Computer Science modified with education and a graduate certificate in secondary school science education from Dartmouth College. Her current research focuses on comparative pathogenesis and response of a diversity of mammalian species to a variety of influenza A viruses, including reconstructed 1918 and 2009 H1N1 pandemic strains. She is interested in influenza receptor identification, viral binding and entry. Additionally, she studies the interspecies variability in host response to influenza A virus via in vivo experimentation, digital and light histopathology, immunohistochemistry and immunofluorescence. Her academic advisors are Jeffery Taubenberger, M.D., Ph.D., J. Mac Law, D.V.M., Ph.D, Dipl ACVP (chair), Mark Simpson, D.V.M., Ph.D, Dipl ACVP and Fred Fuller, Ph.D.



## Co-Infection of *Streptococcus Pneumoniae* Increases Severity of Lung Pathology in 2009 Pandemic Influenza Virus Infected Mice

A. Sally Davis<sup>1,2</sup>, Kash JC<sup>1</sup>, Qi L<sup>1</sup>, and Taubenberger, JK<sup>1</sup>

<sup>1</sup>Viral Pathogenesis and Evolution Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD and <sup>2</sup>Department of Population Health and Pathobiology, North Carolina State University College of Veterinary Medicine, Raleigh, NC

Concurrent and secondary bacterial infections increase disease severity during seasonal influenza viral infections and contributed greatly to increased morbidity and mortality during the 1918, 1957, 1969 and 2009 influenza pandemics. It has been estimated that >95% of the 50 million deaths worldwide during the 1918 influenza pandemic were associated with secondary bacterial pneumonias. Secondary bacterial infections have also been reported as important contributors to death during current 2009 H1N1 influenza pandemic. One of the leading causes of secondary bacterial pneumonias during both seasonal and pandemic influenza viral infections is *Streptococcus pneumoniae* (SP).

To study the effects of secondary bacterial infection during primary influenza virus infection, BALB/c mice were inoculated with 10<sup>5</sup> PFU of a 2009 seasonal H1N1 virus (A/Bethesda/NIH50/09; NIH50) or 2009 pandemic H1N1 virus (A/Mexico/4108/09; Mex09). Two days later, mice were inoculated with 10<sup>5</sup> CFU of type III *Streptococcus pneumoniae* (SP) strain A66.1-Lux expressing luciferase. Three days later, luciferase expression was visualized in live anesthetized mice using a fluorescence imaging system. Lung samples were collected on day 6 Mex09 and NIH50 post viral inoculation for viral titration, histopathology, Gram's staining and immunohistochemical identification of viral antigen distribution.

Mice inoculated with NIH50 or Mex09 showed mild-to-modest weight loss with 100% survival. Histopathologic analysis showed multifocal, mild to moderate, predominantly histiocytic bronchiolitis. Mice inoculated with NIH50 and SP showed increased weight loss with 100% survival. The bronchiolitis in these animal's lungs was multifocal, moderate, more neutrophilic and included adjacent alveolitis. In contrast, mice inoculated with Mex09 and SP showed severe weight loss and 100% mortality by 3-5 days post-bacterial infection. Histopathology revealed multifocal severe necrotizing alveolitis, denuded bronchiolar epithelium and prominent neutrophilic infiltrates.

In contrast with seasonal influenza virus, secondary bacterial infections greatly increased disease severity in 2009 pandemic H1N1 influenza virus infected mice shifting a non-lethal infection into a uniformly lethal disease.



## **Schantel A. Hayes, D.V.M., Diplomate, The American College of Veterinary Pathologists**

Dr. Hayes is a graduate Scholar in the NCI Molecular Pathology Graduate Partnership Program in partnership with Michigan State University and the National Institute of Diabetes and Digestive and Kidney Diseases, from 2005 – present.

Dr. Hayes received her D.V.M. from Tuskegee University in 2004. Dr. Hayes pursued a residency in anatomic pathology in the Department of Pathobiology and Diagnostic Investigation at Michigan State University after graduation. In 2005, she was accepted into the NCI Molecular Pathology Graduate Partnership Program to continue graduate course work and training as a diagnostic pathologist at MSU. Following completion of her diagnostic training and course work, Dr. Hayes accomplished board certification in anatomic pathology by The American College of Veterinary Pathologists in 2007. National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD. Her research focuses on the transcriptional regulation of adipocyte differentiation in a laboratory headed by Elisabetta Muller, Ph.D., within the NIDDK Genetics of Development and Disease Branch. She will complete her dissertation research training in the fall of 2010 and commence employment with Lexicon Pharmaceuticals as a veterinary pathologist in November. Members of her graduate guidance committee include Matti Kiupel D.V.M, Ph.D. (chair), Elisabetta Mueller, Ph.D., James Wagner, M.B.A., Ph.D., and Mark Simpson D.V.M, Ph.D.

**MICHIGAN STATE  
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NATIONAL INSTITUTE OF  
DIABETES AND DIGESTIVE  
AND KIDNEY DISEASES

## ***In vitro* and *in vivo* Characterization of a Novel Regulator of Adipogenesis**

Schantel A. Hayes<sup>1,2</sup>, Sunitha Meruvu<sup>1</sup>, Elisabetta Mueller<sup>1</sup>

<sup>1</sup>Genetics and Development of Disease Branch, The National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Bethesda, MD 20892, <sup>2</sup>Department of Pathobiology and Diagnostic Investigation, College of Veterinary Medicine, Michigan State University, East Lansing, MI

Mesenchymal stem cell differentiation during embryogenesis is a delicate balance of tightly controlled gene expression and transcriptional events driven by a series of transcription factors that lead to the development of muscle, bone, cartilage, and adipose tissue. PPAR $\gamma$  is considered to be the master regulator of the terminal differentiation phase of adipogenesis and functions in a transcriptional cascade that includes members of the CCAT/enhancer binding protein (C/EBP) family of basic helix loop helix transcription factors, and Kruppel like factor family. Although much is known about molecular regulation of the terminal differentiation phase, the transcriptional regulation of early adipogenesis (determination phase) is largely unknown. With this, it is important to study the transcriptional regulation of early adipogenesis and to research novel proteins that may regulate the transcription factors involved in terminal differentiation (PPAR $\gamma$ ).

By candidate gene approach we identified NP220 as a novel regulator of adipogenesis. NP220 is a transcription factor that belongs to the matrin 3 family of nuclear proteins and contains a splicing motif (RS motif), three RNA binding domains (RRM) and a zinc finger domain. We show that NP220 is expressed early in adipocyte differentiation prior to the expression of PPAR $\gamma$  and concomitant with the expression of early regulators, C/EBP $\beta$  and C/EBP $\delta$ . In addition, we demonstrate that NP220 physically interacts with C/EBP $\beta$  and C/EBP $\delta$  and transcriptionally activates PPAR $\gamma$  (Meruvu et al. unpublished data). Forced expression of NP220 in uncommitted mesenchymal cells (10 T1/2 cells) promoted adipogenesis with increased expression of adipocyte specific genes such as PPAR $\gamma$  and aP2. Knockdown of NP220 by small interfering RNAs inhibited fat differentiation and decreased the expression of adipocyte specific genes (Meruvu et al. unpublished data).

To validate the results obtained *in vitro* (in 10 T1/2 cells), a conditional knockdown mouse of NP220 was generated using Cre-LoxP induced RNA interference. The excision of the neocassette was implemented by crossing the NP220 knockdown mouse with transgenic mice that express Cre in the mouse white adipose tissue. Upon U6 promoter activation, 70% reduction of NP220 RNA levels was observed. Analysis of NP220 knockdown mice showed a decrease in body size and consistently and significantly a diminished weight compared to wild type mice at weaning onward. Furthermore, NP220 knockdown showed a significant reduction in visceral, perigonadal and subcutaneous white adipose tissue and percentage of body fat when challenged on high fat diet. Histologic examination of the visceral white adipose tissue depot of NP220 knockdown mice showed that the fat cells contain smaller lipid droplets compared to wild type mice. In addition, mRNA expression levels of key adipocyte genes involved in differentiation, such as PPAR $\gamma$  and C/EBP $\alpha$ , lipid storage and metabolism (adiponectin, leptin, perilipin) were reduced in the visceral depot of NP220 knockdown mice when compared to age and sex matched controls (Hayes et al unpublished data). In conclusion, our *in vitro* and *in vivo* data suggest that NP220 is a critical regulator for white adipocyte development.



## **Yava L. Jones, D.V.M., Diplomate, The American College of Veterinary Pathologists**

Dr. Jones is currently a graduate scholar in the NCI Molecular Pathology GPP in partnership with Michigan State University and the National Cancer Institute, from 2004 – 2006 and 2007 – present.

Dr. Jones obtained a bachelors of arts from Talladega College in 1999 and her doctorate of veterinary medicine from Tuskegee University in 2003. She pursued an anatomic pathology residency at Michigan State University after graduation. In 2004, she was accepted into the NCI Molecular Pathology Graduate Partnership Program to continue her graduate course work and training as a diagnostic pathologist at MSU. Captain Jones interrupted her Cancer Research Training Award training at MSU from 2006-2007 while was deployed to Afghanistan in support of Operation Enduring Freedom with the United States Army Veterinary Corps. Following active duty, she returned to the program and is currently pursuing her Ph.D. dissertation research in the Cancer and Inflammation Program, Center for Cancer Research, at the National Cancer Institute located in Frederick, MD. Dr. Jones' current research topic involves studying the role of Tumor Necrosis Factor- $\alpha$  in the development and propagation of chemically induced colitis and colon cancer using mouse models. Her NIH principal investigator (PI) mentor is Giorgio Trinchieri, M.D. Her graduate committee members include Dr. Trinchieri, Matti Kiupel, Dr. Med. Vet, Ph.D., Diplomate, The American College of Veterinary Pathologists, Vilma Yuzbasiyan-Gurkan, Ph.D., Alison Bauer, Ph.D., and Mark Simpson, D.V.M., Ph.D., Diplomate, The American College of Veterinary Pathologists.



## The Role of TNF and the Microbiota in Acute and Chronic Colitis

Yava L. Jones<sup>1,2</sup>, Amiran Dzutsev<sup>1</sup>, Rosalba Salcedo<sup>1</sup>, Caroline Salter<sup>3</sup> and Giorgio Trinchieri<sup>1</sup>

<sup>1</sup>Cancer and Inflammation Program, Center for Cancer Research, NCI, NIH, Frederick, MD 21702,

<sup>2</sup>Department of Pathobiology and Diagnostic Investigation, Michigan State University, East Lansing, MI,

<sup>3</sup>Laboratory of Cancer Biology and Genetics, NCI, Bethesda, MD

Inflammatory bowel disease (IBD) affects approximately 1.4 million people in the United States. IBD consists of two disorders, ulcerative colitis (UC) and Crohn's disease (CD). CD is a transmural, granulomatous inflammatory condition that can affect any segment of the gastrointestinal tract. This disease is mediated by the effector responses of the T helper (Th)1 and Th17 cells. The disease is lifelong and consists of relapsing and recurring bouts of chronic inflammation. In addition, patients with CD have an increased risk of developing colon cancer.

Tumor necrosis factor (TNF) has been implicated in the development of colitis and as a positive factor in the development of some forms of cancer. This raises the possibility that TNF may play a pro-inflammatory and tumorigenic role in colitis associated cancer. Support of this theory is found in the fact that pharmacological blockade of TNF with monoclonal antibodies has shown great efficacy in reducing inflammation in many patients with CD. Side effects (reactivation of tuberculosis, development of autoimmune diseases, etc.), however, have occurred in small subset of individuals. Also, some patients do not respond to anti-TNF therapy. Thus, elucidation of the exact mechanism of action of the therapy, as well as the differential role of TNF from various cellular sources is needed. Furthermore, the intestinal microbial has been shown to be instrumental in the development and progression of the disease, both in humans and in mouse models of colitis. CD patients with milder forms of the disease have improvement of clinical signs secondary to broad spectrum antibiotic therapy and mice raised under germ free or specific pathogen free conditions have amelioration or decreased disease, respectively.

The haptening agent trinitrobenzene sulfonic acid (TNBS) is a useful model of Crohn's disease in that it elicits a similar cytokine (Th1/Th17 CD 4+ T cell mediated) and inflammatory (transmural, pancolonic, granulomatous) profile as the human disease. This compound can be used to induce acute colitis (via one intrarectal (IR) injection). Chronic inflammation is induced via 5 or 10, weekly IR injections.

Using the model of acute colitis, our studies have shown that, contrary to the chronic condition seen in CD patients, complete abrogation of TNF results in exaggeration of clinical disease and pathology. The cytokine profile induced was consistent with a Th1/Th17 response in WT and TNF<sup>-/-</sup> mice. Notably, however, mRNA levels of INF $\gamma$ , IL-23 $\alpha$ , IL-1 $\alpha$ , and LT- $\alpha$  were higher in TNF<sup>-/-</sup> mice, corresponding with their increase in colitis. In addition, microbial DNA was extracted from fecal samples taken before and either 24 or 48 hours after IR injection. RT-PCR evaluation of many bacterial species that revealed segmented filamentous bacteria (SFB) were increased two-fold in untreated TNF<sup>-/-</sup> mice compared to wild type (WT) littermate controls ( $p < 0.05$ ). Post-treatment, mouse intestinal *Bacteroides* was decreased two-fold in TNF<sup>-/-</sup> mice compared to WT ( $p < 0.001$ ) and SFB were significantly decreased ( $p < 0.001$ ) post-treatment in both WT and TNF<sup>-/-</sup>. These findings indicate that TNF has a protective role in acute colitis and that change in certain components of the intestinal flora (e.g. SFB) may contribute to the severity of the pathology seen in TNF<sup>-/-</sup> mice.

Evaluation of intestinal inflammation and cytokine responses in mice post 5-weekly IR injections revealed that the lack of TNF production also produces a deleterious phenotype. TNF<sup>-/-</sup> had significantly greater weight loss and colitis as compared to WT controls. However, cytokine responses as determined by protein secretion in whole organ cultures were similar between WT and TNF<sup>-/-</sup> mice.

Evaluation of disease in mice treated for 10 weeks is in progress. We hypothesize that the more chronic inflammatory response initiated by 10 IR injections will be decreased in severity in the absence of TNF.

Utilizing mice that have deletion of TNF in enterocytes (E TNF<sup>-/-</sup>), preliminary data indicates that the enterocyte derived source of TNF is sufficient to confer mucosal protection. The lack of enterocyte derived TNF in acute colitis results in recapitulation of the disease seen in TNF<sup>-/-</sup> mice and pathology is significantly greater than in floxed littermate controls. In addition, we also so a significant decrease ( $p < 0.001$ ) in SFB in E TNF<sup>-/-</sup> mice post treatment when compared to littermate controls.

Our findings emphasize the complexity of TNF in promotion and protection during various stages of inflammation, as well as the potential integrated role of the microbiota in promoting or preventing inflammation. In addition, these results underscore the need for a more targeted approach to therapy, rather than broad, long-term blockade of a multifunctional cytokine such as TNF. But also, the need for patient specific therapy driven, at least in part, by the patient's commensal flora may also be beneficial.

*Caroline Salter is a Summer Intern and student at the University of Georgia, College of Veterinary Medicine, Athens, GA*



### **Philip L. Martin, M.S., D.V.M., Diplomate, The American College of Veterinary Pathologists**

Dr. Martin is a graduate scholar in the NCI molecular pathology GPP in partnership with University of Maryland and the National Cancer Institute, 2005 – present.

Dr. Martin received his D.V.M. from Kansas State University in 2003. After completing the D.V.M. Dr. Martin went to the University of California, Davis for residency training in Anatomic Pathology in the Department of Veterinary Pathology. As an anatomic pathology resident Dr. Martin pursued specialty track training in the pathology of laboratory animals and undertook training in the UC Davis Comparative Pathology Laboratory and the Pathology Department of the California Regional Primate Center. In 2005 Dr. Martin began training in comparative pathology through the Graduate Partnership Program at the National Cancer Institute, Bethesda MD. The first year of the GPP program was spent completing graduate course work at the University of Maryland and in additional anatomic pathology training while working in the Comparative Molecular Pathology Unit with Dr. Mark Simpson. Dr. Martin accomplished board certification in Anatomic Pathology by The American College of Veterinary Pathologists in 2006. Dr. Martin is currently pursuing dissertation research in the NCI Cancer and Cell Biology Branch headed by Kathy Kelly, PhD. His Ph.D. dissertation research involves developing an in-vivo bioluminescent transgenic mouse model of prostate cancer metastasis for the purpose of investigating the molecular signaling mechanisms responsible for driving prostate cancer metastasis. Members of his graduate guidance committee include Siba Samal, B.V.Sc., Ph.D., Diplomate, The American College of Veterinary Microbiologists (chair), Xiaoping Zhu, D.V.M., Ph.D., Robert Dooling, Ph.D., Kathy Kelly, Ph.D., and Mark Simpson, D.V.M., Ph.D. Dr. Martin is currently the veterinary pathologist for the NCI Frederick's Center for Advanced Preclinical Research.



## **Bipotential *Pten*<sup>-/-</sup>*P53*<sup>-/-</sup> Prostate Tumor Initiating Cells Give Rise to Adenocarcinoma with Epithelial-to-Mesenchymal Transition, Metastasis, and Androgen Independent Growth**

Philip L. Martin<sup>1</sup>, Rachel M. Pierce<sup>1</sup>, Mark Simpson<sup>2</sup>, and Kathy Kelly<sup>1</sup>

<sup>1</sup>Cell and Cancer Biology Branch, National Cancer Institute <sup>2</sup>Molecular Pathology Unit, Laboratory of Cancer Biology & Genetics, National Cancer Institute. National Institutes of Health, Bethesda, Maryland

The purpose of this study was to develop a mouse model of prostate cancer metastasis that can be used to investigate the molecular properties of the tumor-initiating populations, especially with respect to androgen-dependent regulation and growth. A model was chosen that reflects the genetic alterations of progressive prostate carcinoma in humans. This has been accomplished by first breeding and characterizing a transgenic donor mouse with prostate epithelial specific deletion of two tumor suppressor genes (*Pten* and *TP53*). As with human prostate cancer, donor mice develop prostatic intraepithelial neoplasia (PIN) with progression to adenocarcinoma. However donor mice also develop cancer phenotypes that are rarely observed in human prostate cancer including: spindle cell carcinomas, basal/squamous cell carcinomas and occasionally prostatic urothelial carcinomas. A transgenic mouse with luciferase expression was crossed to this *Pten*<sup>-/-</sup> and *TP53*<sup>-/-</sup> "donor" mouse in order to allow in-vivo bioluminescent monitoring of prostate cancer growth and metastasis in recipient immunocompromised mice. Prostate tumor cells from these "donor" mice were then transplanted into the prostates of immunocompromised recipient mice (orthotopic injection) in order to investigate the in-vivo differentiation of tumor initiating/progenitor cells in their native environment. There was considerable heterogeneity in the tumor phenotype with donor and recipient mice developing varying proportions of adenocarcinoma, basal/squamous carcinoma, spindle cell (sarcomatoid) carcinoma, and prostatic urothelial carcinoma. In order to test the hypothesis that the heterogeneity in tumor phenotype is caused by the transformation of a tumor progenitor (or "stem" cell) that is capable of plasticity and multi-lineage differentiation, clonal cell lines were derived from individual tumor initiating cells from orthotopic prostate carcinomas. Three of these clonal cell lines were selected based on their different in-vitro and in-vivo (subcutaneous tumor assay) characteristics and injected orthotopically in order to investigate their orthotopic differentiation, and to compare their gene expression profiles in the presence of androgen and after androgen withdrawal (simulating the first line of treatment in human prostate cancer). Histopathological analysis of the three different clonal orthotopic tumors has revealed that they differ significantly in several important characteristics including: capability of multi-lineage differentiation (plasticity), metastatic rate, degree of epithelial-to-mesenchymal transition, and androgen sensitivity. In two of the clonal cell lines there was significant in-vivo epithelial-to-mesenchymal transition (EMT) with CK8+ adenocarcinoma losing CK8 expression and gaining vimentin expression during the transition to spindle cell (sarcomatoid) carcinoma. The metastatic rate of these two clonal tumors was very low indicating that EMT is not necessarily required for metastasis. In one of the clonal cell lines which was capable of both luminal and basal cell differentiation in-vivo, there was a high rate of lung and lymph node metastasis. All three of the clonal cell lines were capable of androgen independent growth.

Immunohistochemical (IHC) analysis of these clonal orthotopic tumors demonstrate that the MAP kinase, PI3 Kinase, and AMP Kinase signaling pathways are significantly upregulated in androgen independent growth. A comparison of gene expression profiles between these different clonal tumors is currently underway and is expected to provide more insight into the molecular mechanisms responsible for the important phenotypic differences between the three clones. This analysis is also hoped to identify the cell signaling pathways driving two of the most important events in human prostate cancer: the development of androgen independent tumor growth, and metastasis.



### **Ian N. Moore, D.V.M**

Dr. Moore is a scholar in the NCI Molecular Pathology GPP program in partnership with Michigan State University and the National Institute of Allergy and Infectious Diseases, 2007-current.

Dr. Moore received his DVM from Tuskegee University School of Veterinary Medicine in 2006, and following graduation, entered a residency in Anatomic Pathology the Diagnostic Center for Population and Animal Health, Michigan State University. Following completion of residency training, Dr. Moore is currently a fellow in the NIAID's Laboratory of Infectious Disease (LID) where, under the guidance of Dr. Kanta Subbarao, he studies the pathologic and immunologic responses of the ferret to wild-type Influenza virus infection. Dr. Moore's research interests include mechanisms of infectious disease in animal models.

Dr. Moore's PhD committee is chaired by Kurt Williams DVM, Ph.D., Diplomate, The American College of Veterinary Pathologists.



## Defining the Domestic Ferret Model of Influenza Virus Infection and Disease Pathogenesis

Ian N. Moore<sup>1,2</sup> Kurt J. Williams<sup>2</sup> Kanta Subbarao<sup>1</sup>

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Influenza is an infectious disease caused by negative-sense, single-stranded RNA viruses of the family *Orthomyxoviridae*, which infects both mammals and avian species. Influenza viruses are divided into three distinct groups, which include Influenza A, B and C viruses. Within the Influenza A viruses, there are 16 subtypes of HA (hemagglutinin) and 9 subtypes of NA (neuraminidase) surface proteins. Influenza A viruses of different subtypes can reassort to produce novel progeny viruses. Genetic mutations and the virus' ability to reassort lead to epidemic and pandemic influenza and highlight the need for continued advancement in the areas of vaccine development and disease pathogenesis. The ferret model has been widely used in influenza research; its utility is largely based on the ferret's natural susceptibility to influenza virus infection, clinical disease presentation that is similar to humans, out-bred background that may better represent genetic variation in humans, small size and ease of handling and husbandry, anatomical similarity of the respiratory tract, and highly strain specific antibody responses. Nevertheless, there are limitations of the ferret model, such as inconsistent response to infection with certain subtypes of influenza, poorly defined immunologic data due to a lack of ferret-specific reagents, and variation in clinical disease related to ferret age at the time of infection. In this study we will examine virologic and histopathologic parameters of the ferret model following infection with 3 influenza virus subtypes and their relationship to animal age, virus dose, and volume of inoculum. We will examine the level of virus replication and associated histopathologic changes and immune responses to the 2009 pandemic H1N1 virus, a seasonal human influenza virus (H3N2) and a highly pathogenic avian influenza virus (H5N1) in 8-12 week old and 6-8 month old ferrets. We will administer  $10^6$  or  $10^7$  tissue culture infectious doses (TCID<sub>50</sub>) of virus in volumes of 0.2, 0.5 or 1 ml intra-nasally to lightly anesthetized ferrets and will collect samples from the respiratory tract at several time points post-infection. It is our goal, with investigation and identification of these virus and host factors, to develop a well-defined and robust model of influenza infection that can be applied across the field of influenza virus research.



### **Tanasa S. Osborne, D.V.M.**

Dr. Osborne is a graduate scholar in the NCI molecular pathology GPP in partnership with University of Illinois at Urbana-Champaign and the National Cancer Institute, since 2006.

Dr. Osborne received her D.V.M. from Tuskegee University College of Veterinary Medicine in 2002. That same year, Dr. Osborne entered a combined residency/Ph.D. training program in Anatomic Pathology in the Department of Pathobiology at the University of Illinois at Urbana-Champaign. Upon completion of her residency in 2006 Dr. Osborne began graduate training in comparative pathology through the Graduate Partnership Program at the National Cancer Institute, Bethesda, MD. She is currently pursuing her Ph.D. dissertation research in metastasis biology in the Tumor and Metastasis Section, headed by Chand Khanna, D.V. M., Ph.D., Pediatric Oncology Branch. Her model system includes using a transplantable syngeneic mouse model characterized by orthotopic growth of osteosarcoma in BALB/c mice at appendicular sites with spontaneous metastasis to the lung. The title of her Ph.D. dissertation is "The role of eukaryotic initiation factor 4E (eIF4E) and an enabled translational machinery in osteosarcoma metastasis". Members of her graduate guidance committee including Wanda Haschek-Hock, B.V.Sc., Ph.D., Diplomate, The American College of Veterinary Pathologists (Chair), Chand Khanna, D.V.M., Ph.D., Diplomate, The American College of Veterinary Internal Medicine, Matthew A. Wallig, D.V.M., Ph.D, Diplomate, The American College of Veterinary Pathologists, Lois L. Hoyer, Ph.D., and Timothy M. Fan, D.V.M., Ph.D., Diplomate, The American College of Veterinary Internal Medicine.



## Expression of Eukaryotic Initiation Factor 4E (eIF4E) in Osteosarcoma

Tanasa Osborne<sup>1,3,4</sup>, Ling Ren<sup>1</sup>, Stephen Hewitt<sup>2</sup>, Wanda Haschek-Hock<sup>3</sup>, and Chand Khanna<sup>1</sup>

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The most significant problem for cancer patients is the dissemination of cancer cells and the formation of metastatic disease. Emblematic of the problem is the clinical progression seen in most patients with osteosarcoma, where metastasis to the lung is the most common cause of death. Cancer cells are believed to efficiently regulate protein translation at specific times and locations in a cell in response to changes in their environment. Preventing the dynamic regulation of these proteins (many of which have been associated with cancer) may be an effective treatment strategy in the management of metastasis. Within the process of protein translation the abundance and activation of the mRNA cap-binding phosphoprotein, eukaryotic initiation factor 4E (eIF4E) is considered to be both rate and process limiting. Our goal is to define the biological role of eIF4E in the metastatic phenotype of osteosarcoma, in hopes of directly or indirectly inhibiting eIF4E expression as a means to treat osteosarcoma. We will employ a comparative approach to study the biology of metastasis in osteosarcoma by using tissues and reagents from murine and human osteosarcomas. Recently, we confirmed high and consistent expression of eIF4E in human osteosarcoma tissues and demonstrated our ability to detect and stably overexpress and knockdown eIF4E protein in a variety of osteosarcoma cell lines. We propose to modulate eIF4E expression in murine and human osteosarcoma cell lines using overexpression and knockdown techniques to define the role of eIF4E at various steps of the metastatic cascade *in vitro* and *in vivo*.



## **Heather R. Shive, D.V.M., Diplomate, The American College of Veterinary Pathologists**

Dr. Shive is currently a graduate scholar in the NCI molecular pathology GPP in partnership with the University of Maryland and the National Cancer Institute, from 2006 to present.

Dr. Shive received her D.V.M from North Carolina State University, College of Veterinary Medicine in 2004. Following graduation, she joined the residency program in Anatomic Pathology in the Department of Pathobiology at Texas A&M University, College of Veterinary Medicine. She trained for two years as a resident at TAMU, and was accepted as a graduate fellow in molecular pathology through the Graduate Partnership Program at the National Cancer Institute in 2006. Dr. Shive was concurrently accepted into the graduate program at the University of Maryland through the GPP. While pursuing graduate training at the NCI, she achieved board certification in Anatomic Pathology by the American College of Veterinary Pathologists in 2007. Dr. Shive is currently completing her dissertation research in the research laboratory of Dennis Hickstein, M.D., in the Experimental Transplantation and Immunology Branch at the NCI. The dissertation project has focused on investigating germline mutations in the breast cancer-2 gene (*brca2*) in the zebrafish (*Danio rerio*). These studies have revealed a critical role for *brca2* in ovarian development, and provide new insights into *brca2* mutation and cancer susceptibility. Members of her graduate guidance committee include Siba Samal, BVSc, Ph.D., Diplomate, The American College of Veterinary Microbiologists (chair), Dennis Hickstein, M.D., Paul Liu, M.D., Ph.D., Mark Simpson, D.V.M, Ph.D., Diplomate, The American College of Veterinary Pathologists, Liangli Yu, Ph.D., and Xiaoping Zhu, D.V.M, Ph.D.



## Modeling Germline *brca2* Mutations in Zebrafish

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<sup>1</sup>Experimental Transplantation and Immunology Branch, NCI, NIH, Bethesda, MD; <sup>2</sup>Department of Veterinary Medicine, University of Maryland, College Park, MD, <sup>3</sup>Department of Molecular Biosciences, The University of Kansas, Lawrence, KS; <sup>4</sup>Genetics and Molecular Biology Branch, NHGRI, NIH, Bethesda, MD

Women with mutations in the breast cancer associated gene-2 (*BRCA2*) are predisposed to ovarian cancer; however, the role for *BRCA2* in carcinogenesis and the link between *BRCA2* mutation and ovarian cancer susceptibility are undefined. Epidemiologic evidence suggests that mutations in the “ovarian cancer cluster region” in *BRCA2* exon 11 are associated with an increased incidence of ovarian cancer relative to breast cancer in affected families. *In vivo* studies of *BRCA2* mutation in mouse models are limited, as gene targeting leads to embryonic lethality in most instances.

To investigate the role of *brca2* in development and tumorigenesis, we established a zebrafish line with a nonsense mutation in *brca2* exon 11 (*brca2*<sup>Q658X</sup>), a mutation similar in location and type to *BRCA2* mutations in humans with hereditary breast and ovarian cancer. Unlike mouse models, *brca2*<sup>Q658X</sup> homozygotes were viable and survive to adulthood. However, all *brca2*<sup>Q658X</sup> homozygotes developed as infertile males with failure of meiotic progression and germ cell apoptosis in the testes. Thus, *brca2* loss in the adult zebrafish testis results in incomplete spermatogenesis, meiotic arrest, and spermatocyte apoptosis.

To determine how *brca2* mutation prevents ovarian differentiation in zebrafish, we analyzed gonad development in juvenile zebrafish. Although wildtype juvenile zebrafish normally undergo immature ovary development before definitive sexual differentiation, our analyses revealed that juvenile *brca2*<sup>Q658X</sup> homozygotes did not form ovaries. Failure of ovarian development in *brca2*<sup>Q658X</sup> homozygotes appeared to arise from altered signaling between primordial germ cells and gonadal stromal cells, since germ cell migration to the embryonic gonadal ridge was unimpaired in *brca2*<sup>Q658X</sup> homozygotes. Ovarian development in *brca2*<sup>Q658X</sup> homozygotes was rescued by homozygous *tp53* mutation, reflecting the importance of germ cell apoptosis in gonad morphogenesis.

In adulthood, *brca2*<sup>Q658X</sup> homozygous zebrafish are predisposed to testicular neoplasias. Additionally, tumorigenesis in multiple tissues is significantly accelerated by concomitant homozygous *tp53* mutation in both *brca2*<sup>Q658X</sup> homozygous and *brca2*<sup>Q658X</sup> heterozygous zebrafish. These findings suggest a specific role for *brca2* mutation in gonadal tumors, and imply collaborative effects of *tp53* and *brca2* mutations on tumorigenesis.

These studies reveal critical roles for *brca2* in zebrafish ovarian development and spermatogenesis. Furthermore, we demonstrate that the propensity for tumorigenesis in reproductive tissues in association with *brca2* mutation appears to be conserved in zebrafish. In humans, the role for *BRCA2* in ovarian development and the effects of *BRCA2* mutation on intercellular signaling in the gonad are not known; thus, the implications for *BRCA2*-associated ovarian cancer are as yet unclear. However, these observations provide new insights into how germ cell-stromal cell interactions in the ovary may relate to cancer susceptibility.



### **Heather S. Tillman, D.V.M**

Dr. Tillman is currently a graduate scholar in the NCI Molecular Pathology GPP in partnership with the Michigan State University and the National Cancer Institute, beginning 2008.

Dr. Tillman received her D.V.M. from the University of Georgia in May, 2008. She is currently in her third-year of training as a graduate scholar in comparative pathology at the National Cancer Institute, where she is completing her dissertation research and training in pathology. Her research interests are in cancer biology, proteomics, and the development of animal models of human disease. Her academic advisor is Matti Kiupel, Dr. Med. Vet., Ph.D., Diplomate, The American College of Veterinary Pathologists.



## ***In vitro* and *in vivo* expression of primary cilia in two murine prostate cancer epithelial luminal cell lines and corresponding orthotopic tissue sections**

Heather S. Tillman<sup>1,3</sup>, Wassim G. Abou-Kheir<sup>2</sup>, Philip Martin<sup>2</sup>, Rachel Pierce<sup>2</sup>, & Kathleen Kelly<sup>2</sup>

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Over the past two decades the physiological & pathological roles of primary cilia in developmental biology, genetic diseases, & cancer has become clearer. Primary cilia are mechanosensory and chemosensory organelles that are instrumental for appropriate vertebrate development, cell polarity, and environmental homeostasis. Many signaling pathways, such as the Sonic hedgehog (Shh), Wnt, and PDGFR $\alpha$  pathways are effected by the presence and characteristics of primary cilia as a result of these cell surface signaling pathways being localized to the primary cilia. Aberrant signaling and disruption of cilia formation results in altered regulation of the cell-cycle and uncontrolled proliferation that manifests as developmental malformations, genetic diseases, or neoplasia. Primary cilia have only been documented in mouse urogenital sinus stromal cells but not extensively studied in prostate carcinomas, although Shh signaling has been implicated in prostate cancer progression. In other epithelial neoplasms studies have documented a notable decrease in numbers or complete absence of primary cilia in increasingly malignant phenotypes. There are also concurrent alterations in Shh, Wnt, and PDGFR $\alpha$  signal transduction. We have established and characterized a panel of prostate tumor-derived cell clones from *Pten/Tp53* deleted prostate adenocarcinomas. We have determined using microarray data comparing orthotopic prostate tumors developed from the above cell lines growing under androgen replete or deprived conditions that a variety of primary ciliary components are upregulated upon androgen deprivation. We have established the presence of primary cilia in prostate epithelial tumor cells by both immunocytochemistry and immunohistochemistry using an antibody to acetylated-alpha tubulin. This novel finding provides a model and mechanistic approach to study the role of primary cilia both *in vitro* & *in vivo* in prostate cell signaling, androgen-responsiveness, and cancer progression.



### **Kevin D. Woolard, D.V.M.**

Dr. Woolard is a graduate scholar in the NCI Molecular Pathology GPP in partnership with the North Carolina State University and the National Cancer Institute, from 2003 - present.

After graduating from veterinary school at North Carolina State in 2003, Dr. Woolard stayed at the College of Veterinary Medicine, entered the molecular pathology GPP as a Cancer Research Training Fellow and undertook graduate course work and training in anatomic pathology. During his diagnostic pathology training he formed an interest in neuro-pathology and in neural stem cell biology. Following these interests, he is currently completing his Ph.D. dissertation research into the comparative genomics driving canine and human gliomagenesis, and focusing on the establishment of the dog as a spontaneous model for human gliomagenesis. Additionally, by comparing canine and human glioma stem cells to physiologic embryonic and adult canine neural stem cells, we hope to elicit signaling pathways involved in self-renewal commonly expressed in both populations. The dog represents a unique opportunity for meaningful comparative research of this spontaneous, heterogeneous tumor in humans through its remarkable genetic and physiologic similarity to human disease. Through comparative genomic analysis and investigation into self-renewal signaling pathways shared between human and canine glioma stem cells, and ultimately canine embryonic stem cells, we hope not only to better understand the process of glioma development and progression, but also to identify future molecular targets for therapeutic intervention.



Dr. Woolard is a member of the Neuro-Oncology Branch, headed by Howard A. Fine, M.D. Other members of his graduate committee include John Cullen, V.M.D., Ph.D. Diplomate, The American College of Veterinary Pathologists (chair), Matthew Breen, Ph.D., Dave Malarkey, D.V.M., Ph.D., Diplomate, The American College of Veterinary Pathologists, and Mark Simpson D.V.M., Ph.D., Diplomate, The American College of Veterinary Pathologists.

## **Comparative Genomics of Canine and Human Glioma Stem Cells: The Dog Faithfully Recapitulates Genomic Alterations Driving Human Glioblastoma**

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Mariam Totonchy<sup>1</sup>, Maggie Cam<sup>1</sup>, Myung jin Son<sup>1</sup>, Maureen Beederman<sup>1</sup>,  
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Despite aggressive multimodality treatment, the overall prognosis for patients with high-grade gliomas (anaplastic astrocytomas and glioblastoma multiforme (GBM)) remains very poor, with median survival times of those suffering from GBM less than 14 months. To date, in spite of widespread and intensive investigation regarding the biology of so-called glioma tumor stem cells or glioma stem cells (GSCs) disappointingly little progress has been achieved in translational medicine or in our understanding of the formation and progression of glioma tumors to date. Confounding attempts at dissecting the complex genomic aberrations in human GBMs is the fact that these tumors often develop pronounced, large regions of chromosomal amplification or deletion, frequently involving entire chromosomal arms, in which we are only able to ascribe significant tumor suppressor or oncogene function to a single gene within this large region. In the face of such a complex, heterogeneous genome, efforts at modeling glioblastoma biology in genetically engineered mouse models by deleting or amplifying single genes or small clusters of genes often fails to recapitulate the behavioral, phenotypic, or genomic heterogeneity of spontaneous human glioblastoma tumors. Currently, there is no validated, naturally occurring model for human gliomagenesis. The domestic dog recapitulates every human histologic grade and develops glioma at an equivalent incidence to humans and as such, represents the only feasible model for comparative study of spontaneously occurring glioma tumors.

Here, we have characterized the dramatic similarities between glioma stem cells (GSCs) isolated from a canine anaplastic astrocytoma and our human GSC lines, and follow the canine GSCs as they form serial, orthotopic xenografts in immunocompromised mice. Remarkably, serial xenotransplantation of our canine GSCs results in a progressive increase in tumor malignancy, expansion of the GSC subpopulation, and progressive genomic alterations strikingly similar to those associated with human secondary GBM formation. Chiefly, canine GSCs exhibit deletions of p16/ARF, loss of PTEN, and loss of p53 function through amplification of MDM2 and MDM4.

In addition to the identification of these copy number alterations (CNAs) present in our canine GSCs over serial xenotransplantation, analysis of the comparative genomic alterations between canine and human GSCs identifies numerous additional, putative tumor suppressor genes across both species. The canine genome is organized into 38 autosomes compared to the human 22, resulting in the dispersion of human chromosomal regions across multiple syntenic canine genomic segments occupying numerous individual chromosomes. Thus, the genomic sequence of any particular human chromosome corresponds to many, separate or segmented canine chromosomes. This is significant because in comparing the exact chromosomal regions altered in both species we are able to focus on small, highly conserved regions containing tumor suppressor or oncogenes we believe may be relevant to human glioma biology. As mentioned previously, our canine GSC samples contain deletion of the terminus of canine chromosome 26 (cfa26), a region containing PTEN (located on hsa10q23.3).

However, these canine GSCs also exhibit progressive deletion of portions within cfa4, a region syntenic to hsa10q21-hsa10q23, directly upstream of the PTEN locus. The co-deletion of these two canine chromosomal segments containing adjacent syntenic regions on hsa10q indicate that additional tumor suppressor genes aside from PTEN may be located within this region. Indeed, the co-deleted region of cfa4 contains several genes of suspected tumor suppressor function or in pathways known to be vital in human glioma, including ANXA7, CCAR1, and BMPR1a.

Global analysis of copy number alterations found in our canine GSCs shows additional regions commonly altered in human glioblastoma, including hsa6q and hsa7. Further examination of the genomic alterations involved in canine gliomagenesis will not only serve to validate the molecular basis of the dog as a comparative model for spontaneous glioma, but also identify genes of biologic value in the formation and progression of both canine and human glioma.



### **Leah Zadrozny, D.V.M**

Dr. Zadrozny is currently a graduate scholar in the NCI Molecular Pathology GPP in partnership with North Carolina State University and the National Heart, Lung, and Blood Institute, beginning 2008.

Dr. Zadrozny received her D.V.M. from North Carolina State University in May, 2008. She has recently completed her second-year of training as a graduate scholar in comparative pathology at the NCSU College of Veterinary Medicine, where she focused on training in diagnostic pathology and graduate course work. Her research interests are in modeling the functional pathophysiology of cardiovascular disease, with an emphasis on atherosclerosis, with her Ph.D. dissertation studies planned in the NHLBI Laboratory of Cardiac Energetics headed by Robert Balaban, Ph.D. Her academic advisors are John Cullen, V.M.D., Ph.D., Diplomate, The American College of Veterinary Pathologists, Keith Linder, D.V.M., Ph.D., Diplomate, The American College of Veterinary Pathologists, and Mac Law, D.V.M., Ph.D., Diplomate, The American College of Veterinary Pathologists.



## Spontaneous Hepatocellular Carcinoma in Captive Prosimians: Investigations and Pathogenesis

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Spontaneous hepatocellular carcinoma has been reported as a relatively common neoplasm in prosimians. However, the cause is unknown. To investigate possible pathogenic mechanisms, a review was performed of all adult animals that had postmortem examinations over the last 10 years from a captive prosimian population. A detailed histologic evaluation was done of all suspected proliferative liver lesions. Hepatocellular carcinoma was diagnosed in 14/145 (9.7%) lemurs. Affected animals ranged between the ages of 6 to 40 years old. These tumors had an unusually aggressive growth pattern for animal species, as metastasis to the lungs or mediastinum was evident in 7/14 (50%) animals. Thirty-one animals, 9 with hepatocellular carcinomas and 22 age-matched controls without hepatic neoplasia, were tested to evaluate the relationship between hepatic iron stores, as well as other trace metals, and the presence of hepatocellular carcinoma. There was no difference between the hepatic iron, copper, or molybdenum in lemurs with hepatocellular carcinoma and those without, suggesting that iron is not a key element in the pathogenesis of liver tumor formation. Analysis of 22 serum samples from animals with or without liver tumors indicated that there was no evidence of active infection with a hepadnavirus, the virus family that includes hepatitis B virus, in the livers of normal animals or those with liver tumors.

A subset of this prosimian population affected with hepatocellular carcinoma, including 6 exhibiting metastasis and 3 without, with the addition of 11 age-matched controls, were further examined to determine a potential pathogenic role of *H-ras* mutations. A total of 26 liver samples including 11 normal livers, 9 with hepatocellular carcinoma, and 6 samples from non-neoplastic regions of liver from animals with hepatocellular carcinoma were evaluated. In doing so, a consensus sequence for exons 1 and 2 of *H-ras* in prosimians was determined and considered identical to that of human *H-ras* and differing only slightly from the chimpanzee sequence. Point mutations were identified in 6 of the 9 hepatocellular carcinoma samples examined with codons 7, 22, 32, 56, 61, 84 and 96 affected. Two carcinomas had double mutations and one tumor had triple mutations. One hepatocellular carcinoma had a mutation in codon 61, which is identical to a recognized affected codon for a *H-ras* "hot spot" in rodent neoplasia that has also been reported in human tumors. Although not statistically significant, metastasis occurred in 5/6 (83%) hepatocellular carcinomas with *H-ras* mutations and only 1 of 3 hepatocellular carcinomas without mutations. There were 4 silent mutations which did not contain changes in the encoded amino acids, two of which were found in non-neoplastic regions of tumor-bearing liver.

In conclusion, the pathogenesis of hepatocellular carcinoma in prosimians remains unclear. There was no evidence of active hepadnavirus (hepatitis B virus family) infection in prosimians with hepatocellular carcinoma, nor was there a detectable relationship between hepatic iron levels and the incidence of liver tumors. In a subsequent study, although more than 83% of the animals with the mutation in *H-ras* and 1 of 3 without the gene developed metastasis, the difference in proportion with metastasis was not statistically significant. The functional consequences of the *H-ras* mutations identified remain unclear. However, the determination of an identical consensus sequence for exons 1 and 2 of *H-ras* for prosimians and humans may provide insight into the role of *H-ras* mutations and their relevance to human cancer.

**Biographies and Research Abstracts  
(Trainees on University Campuses)**





### **Joy Gary, D.V.M**

Dr. Gary is currently a graduate scholar in the NCI Molecular Pathology GPP in partnership with Michigan State University and the National Cancer Institute, beginning 2009.

Joy Gary grew up in Colorado and attended Davidson College in North Carolina. She received her DVM from Colorado State University in 2009. She is currently completing a residency in Veterinary Anatomic Pathology at Michigan State University, and is a graduate scholar in the Comparative Molecular Pathology program through the National Cancer Institute and Michigan State University.



## Staphylococcal Enteritis (Similar to Sticky Kit Syndrome) in Ferret Kits

J. Gary<sup>1,2</sup>, I. Moore<sup>2,3</sup>, I. Langohr<sup>2</sup>, and M. Kiupel<sup>2</sup>

<sup>1</sup>Diagnostic Center for Population and Animal Health, Michigan State University, East Lansing, MI,

<sup>2</sup>Comparative Molecular Pathology Unit, Laboratory of Cancer Biology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, and <sup>3</sup>Laboratory of Infectious Disease, National

Institutes of Allergy and Infectious Diseases, National Institute, NIH, Bethesda, MD

Sticky kits syndrome, a pre-weaning mucoid diarrhea in 10-14 day-old mink kits, has recently been associated with intestinal colonization by enterotoxigenic *Staphylococcus delphini*, with no associated inflammation or villous destruction. A similar condition was recently observed in four, 3 to 4 week-old ferret kits that were submitted for necropsy to the Diagnostic Center for Population and Animal Health at Michigan State University. Grossly, multiple bowel loops in all ferrets were moderately distended by mucoid to liquid contents. Histologically, myriads of gram-positive, coccoid bacteria colonized variable segments of the small intestine. The colonizing bacteria were phenotypically identified as belonging to the *Staphylococcus intermedius* group of bacteria. Nucleic acid sequence analysis of the 16S ribosomal RNA gene as well as further nucleic acid sequencing of polymerase chain reaction (PCR) amplicons from the superoxide dismutase gene and the heat shock protein gene are in progress to further characterize the isolate. Though few outbreaks of food poisoning have been attributed to *S. intermedius*, recent studies have shown that 90% of animal isolates of *S. intermedius* produced enterotoxins. Interestingly, *S. aureus*, the staphylococci most commonly associated with enterotoxigenesis, has also been shown to colonize the intestine of humans and mice similar to the *Staphylococcus* sp. in our ferrets. While direct causation has not been confirmed, we postulate that the observed hypersecretory diarrhea in these ferret kits was the result of small intestinal colonization by *Staphylococcus* sp. with the subsequent production of enterotoxin. Experimental reproduction of the described syndrome is currently in progress.



### **Tiffany Reed, D.V.M.**

Dr. Reed is currently a graduate scholar in the NCI Molecular Pathology GPP in partnership with Purdue University and the National Cancer Institute, beginning 2009.

Dr. Reed received her D.V.M. from the University of Georgia in 2008, and following graduation entered a 3-year anatomic pathology residency at Purdue University's Animal Disease Diagnostic Laboratory. Following one year of training, Dr. Reed entered the Molecular Pathology GPP as an NCI Cancer Research Training Fellow. She will complete her diagnostic pathology training and graduate coursework this 2010-2011 academic year. Dr. Reed's research interests include mechanisms of carcinogenesis, pathways of metastasis, and diagnostic and molecular imaging, specifically in renal, prostate, or mammary cancers. Her academic program advisors are Dr. Margaret A. Miller, D.V.M., Ph.D., Diplomate, The American College of Veterinary Pathologists, Dr. José Ramos-Vara, D.V.M., Ph.D., Diplomate, The European College of Veterinary Pathologists, and Dr. Stephen Lenz, D.V.M., Ph.D., Diplomate, The American College of Veterinary Pathologists.



## Spread of Transitional Cell Carcinoma to Urine-Scalded Inguinal Skin in a Collie Dog

L.T. Reed<sup>1,3</sup>, M. Childress<sup>2</sup>, D.W. Knapp<sup>2</sup>, H.L. Thacker<sup>1</sup>, M.A. Miller<sup>1</sup>

<sup>1</sup>Animal Disease Diagnostic Laboratory and Department of Comparative Pathobiology, and

<sup>2</sup>Department of Veterinary Clinical Sciences and School of Veterinary Medicine, Purdue University, West Lafayette, IN, <sup>3</sup>Laboratory of Cancer Biology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD

An 11-year-old, spayed female Collie dog had a 7-month history of treatment for urinary bladder and urethral transitional cell carcinoma (TCC), with a 6-week history of weakness and urinary incontinence and a 1-week history of hind limb proprioceptive deficits. Ventral abdominal and inguinal skin was reddened, hyperpigmented, and thickened; methicillin-resistant *Staphylococcus aureus* was isolated from cutaneous

swabs one and two months before the dog's death. One month before death, pyoderma and carcinoma were diagnosed histologically from a biopsy specimen of inguinal skin. Numerous neoplastic epithelial cells, some with large (30- $\mu$ m diameter), unstained cytoplasmic vacuoles, were identified in the dermis, including within lymphatic vessels, and abutting the focally ulcerated epidermal surface. The dermis was edematous and

diffusely infiltrated by neutrophils, macrophages, and histiocytes; where intact, the epidermis was acanthotic and hyperkeratotic. At necropsy, transitional cell carcinoma was still present in the inguinal skin, urinary bladder and urethra, and had metastasized to lung, intestine, and adrenal gland. The reported neurologic signs were attributed to axonal degeneration of unknown cause in the cervical and lumbar spinal cord. Cutaneous involvement by TCC is uncommon and thought to be associated with retrograde lymphatic metastasis or implantation during abdominal surgery; however, this dog had not had abdominal surgery during the diagnosis or treatment of TCC. The authors speculate that transitional cell carcinoma spread to inguinal skin in this case either via lymphatic vessels or by transepidermal extension in urine-scalded skin.



**Laura Baseler, M.S., D.V.M.**

Dr. Baseler is currently a graduate scholar in the NCI Molecular Pathology GPP program in partnership with Purdue University and the National Institute of Allergy and Infectious Diseases, beginning July 2010.

Dr. Baseler received her M.S. in Meat Science in 2009 and her D.V.M. in 2010 from Iowa State University. She began her pathology residency and graduate fellowship in July of 2010 at Purdue University. After completion of the initial graduate educations and residency portion of the program, she will be relocating to Hamilton, MT to begin research on highly pathogenic viruses, with Heinz Feldmann, M.D., Ph.D., at the National Institute of Allergy and Infectious Diseases, Rocky Mountain Laboratories.





### **Kara N. Corps, D.V.M., M.S.**

Dr. Corps is a graduate scholar in the NCI Molecular Pathology GPP in partnership with North Carolina State University and the National Institute of Neurological Disorders and Stroke, beginning in July 2010.

After completing the didactic portion of veterinary school, Dr. Corps spent 2008 working towards a M.S. in Comparative Medicine and Integrative Biology under Jack Harkema, D.V.M., Ph.D., Diplomated, ACVP at Michigan State University. She defended her thesis MS in December 2008. Dr. Corps received her D.V.M. from Michigan State University in May 2010. Dr. Corps is currently an Anatomic Pathology resident at North Carolina State University and is interested in neuroimmunology. She will pursue Ph.D. her research training through the National Institute of Neurological Diseases and Stroke.





### **Amy C. McCalla-Martin, D.V.M.**

Dr. McCalla-Martin is a first year graduate scholar in the NCI molecular pathology GPP in partnership with North Carolina State University and the National Cancer Institute.

Dr. McCalla-Martin received her BS in Microbiology and Molecular Cell Sciences from The University of Memphis in 2001. Following this degree she was a member of Dr. Stephen Skapek's lab at St. Jude Children's Research Hospital until 2004. During this time she developed two *Arf* transgenic mouse models as well as an *Arf* null knock-out mouse model. She coauthored four publications with the Skapek lab and was the primary author on an additional publication. Research undertaken in this lab examined the role of p19Arf in vascular remodeling and development of the disease persistent hyperplastic primary vitreous.

In 2005, Dr. McCalla-Martin joined Dr. Jorge Piedrahita's lab at North Carolina State University. She coauthored two publications with this lab on research involving porcine microarray systems and the correlation between intrauterine growth restriction and somatic cell nuclear transfer techniques in swine. In January of 2010, she was primary author on a publication through this lab which described the *Gli2* transgenic pig.



Dr. McCalla-Martin began the DVM program at NCSU in the fall of 2006. During her DVM program she continued to work with the Skapek and Piedrahita labs and presented research from both labs at the annual ACVP conferences in 2007 and 2008. She is currently a first year anatomic pathology resident, graduate fellow at NCSU-CVM. In May of 2012 she will transition to Bethesda, MD for completion of graduate training in comparative molecular pathology through the Graduate Partnership Program at the National Cancer Institute.



# **Training Program Mentors**



# ***Training Program Directors, Faculty Major Professors, and NIH Mentors***

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**Wanda Haschek-Hock, D.V.M., Ph.D.**

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Professor Emeritus, University of Illinois at Urbana-Champaign

**Siba K. Samal, B.V.Sc., Ph.D.**

Diplomate, The American College of Veterinary Microbiologists  
Professor and Associate Dean, University of Maryland

***List of Participating NIH Mentor and University Major Professors,  
with Veterinary Pathologists who are Conducting Dissertation Research***

**Howard Fine, M.D.**

Senior Investigator, Neuro-Oncology Branch, CCR, NCI and NINDS

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*Graduate Scholar*

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**Kathy Kelly, Ph.D.**

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**Chand Khanna, D.V.M., Ph.D.**

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**Ian Moore, D.V.M.**

**Dissertation Laboratory To Be Determined**

National Cancer Institute

**Matti Kiupel, Dr. Med. Vet., Ph.D.**

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Associate Professor, Michigan State University

*Graduate Scholar*

**Heather Tillman, D.V.M.**

**Robert Balaban, Ph.D.**

Scientific Director of Laboratory Research, Division of Intramural Research,  
Senior Investigator, Laboratory of Cardiac Energetics, NHLBI

**John Cullen, V.M.D., Ph.D.**

Diplomate, The American College of Veterinary Pathologists  
Professor, North Carolina State University

*Graduate Scholar*

**Leah Zadrozny, D.V.M.**

**2010 Veterinary Student CBSTP  
Travel Award Recipients and  
Submitted Abstracts**



## ***Travel Award Recipients***

- 1. Claire Fellman (DVM Candidate)**  
Mississippi State University, College of Veterinary Medicine
- 2. Tim Kurt (DVM/PhD Candidate)**  
Colorado State University, College of Veterinary Medicine and Biomedical Sciences
- 3. Noelle M. Knight (VMD/PhD Candidate)**  
University of Pennsylvania, School of Veterinary Medicine
- 4. Jeffrey Norris, Ph.D. (DVM Candidate)**  
University of California, Davis, School of Veterinary Medicine
- 5. Caroline Piskun (DVM Candidate)**  
University of Wisconsin, School of Veterinary Medicine
- 6. Michelle Cook Sangar (VMD/PhD Candidate)**  
University of Pennsylvania, School of Veterinary Medicine
- 7. Ashley Talley (DVM Candidate)**  
Kansas State University, College of Veterinary Medicine
- 8. Lei Wang (DVM/PhD Candidate)**  
University of Illinois, College of Veterinary Medicine
- 9. Koji Yasuda (DVM Candidate)**  
Cornell University, College of Veterinary Medicine

# ***Travel Award Recipients' Submitted Abstracts***

**Claire Fellman**

## **Effects of Different Oral Doses of Cyclosporine on T-Lymphocyte Biomarkers of Immunosuppression in Normal Dogs**

C Fellman, T Archer, J Stokes, L Pinchuk, C Langston, K Lunsford, A Mackin

Mississippi State University, College of Veterinary Medicine, Mississippi State, MS

Cyclosporine is a potent immunosuppressive agent used to treat many canine diseases. Optimal dosing regimens remain unclear, primarily because standard methods that monitor effectiveness of immunosuppression have not been established. Our study was designed to evaluate a comprehensive panel of biomarkers of immunosuppression in seven normal dogs at two different oral doses of cyclosporine. We used flow cytometry to measure expression of cytokines (IL-2, IL-4, and INF- $\gamma$ ) and surface antigens (CD25 and CD95) on T-lymphocytes activated with PMA/ionomycin and concanavalin A. Dogs were first given a high dose of cyclosporine sufficient to reach immunosuppressive trough drug blood levels of at least 600 ng/mL (measured by HPLC). Biomarkers were evaluated on Day 8 of treatment, 8 hours after dosing. Expression of cytokines IL-2 and INF- $\gamma$  was significantly reduced from baseline levels in all dogs, whereas results with cytokine IL-4 and surface markers CD25 and CD95 were more variable. After a washout period, dogs were given cyclosporine at the dose approved to treat atopy (5mg/kg sid), and expression of IL-2 and INF- $\gamma$  was again measured. INF- $\gamma$  mean T-lymphocyte fluorescence was significantly decreased, but IL-2 data only trended to decrease.

Suppression of cytokine expression was less marked at the lower dose of cyclosporine, and more variable in individual dogs. Our study confirms that cyclosporine suppresses selected biomarkers of immunosuppression in a dose-dependent manner. Further investigation of the effects of cyclosporine on these biomarkers in normal dogs at different doses and blood levels of the drug, and in clinic patients, is warranted.

*Research Support: ACVIM Foundation and Dr. Hugh Ward Discretionary Fund*

*Student Support: Morris Animal Foundation Veterinary Student Scholars Program*

**Tim Kurt**

## **Enhanced Transmission of Chronic Wasting Disease Prions to Non-Cervid Species by Amplification In Vitro**

Timothy Kurt, Davis Seelig, and Edward Hoover

Colorado State University, College of Veterinary Medicine and Biomedical Sciences, Fort Collins, CO

**Background:** Chronic Wasting Disease (CWD) is an efficiently transmitted prion disease of cervids. Whether CWD could represent a threat to non-cervid species remains unknown. We amplified CWD prions *in vitro* using protein misfolding cyclic amplification (PMCA) and brain substrates from several non-cervid species to evaluate whether PMCA could be used to predict susceptibility to CWD.

**Methods:** We diluted CWD prions from infected deer into brain substrate from non-cervids. The samples were sonicated and incubated for 48 hrs, then analyzed by western blotting. Samples

containing newly formed protease-resistant prions were used to inoculate prairie voles. Upon euthanasia, brains were removed and evaluated for evidence of prions by western blotting and immunohistochemistry.

**Results:** Amplification of CWD prions in brain from non-cervids was associated with *in vivo* susceptibility and the presence of asparagine at amino acid position 170 of the substrate precursor protein. Prairie voles inoculated with prions from the PMCA assay developed disease more rapidly than those inoculated with CWD prions not subjected to PMCA. Clinical signs and protease-resistant prions were absent in control animals.

**Conclusion:** We have demonstrated that PMCA can be used to predict susceptibility to CWD and that ability to support PMCA is associated with the presence of asparagine at position 170 of the substrate precursor protein. Furthermore, we found that PMCA enhances transmission of CWD to prairie voles. Interestingly, vole-prions amplified in more species than cervid-origin prions, which suggests that the infectious agent has increased host-range. These results enable us to better understand CWD species barriers and spread.

## Jeffrey Norris

### A Novel Platelet Signaling Defect Causes Bleeding in Horses

Jeffrey Norris, Monica Pombo, Elena Shirley and Fern Tablin

University of California, Davis, School of Veterinary Medicine, Davis, CA

Platelets are anucleate cells, derived from megakaryocytes, that function to coordinate hemostasis through the tightly regulated secretion of cofactors required to catalyze the polymerization of fibrinogen. This secretion system relies on a primary signaling pathway induced by thrombin and secondary “outside-in” signaling by the major platelet fibrinogen receptor, the  $\alpha$ IIb- $\beta$ IIIa integrin. We have identified a group of horses with prolonged template bleeding times that have a 90% reduction in platelet-dependant fibrinogen polymerization, subsequent to platelet stimulation with thrombin, as compared to controls, *in vitro*. In response to thrombin, platelets from these horses also have diminished secretion of Factor V, a key cofactor in the fibrinogen polymerization reaction. Secretion of platelet  $\alpha$ -granules containing Factor V depends on phosphorylation of Akt, which is also diminished relative to control levels in thrombin treated platelets from affected horses. However, Akt phosphorylation in platelets from affected horses appears normal after concurrent treatment with thrombin and the  $\alpha$ IIb- $\beta$ IIIa integrin blocking peptide RGDS. Since RGDS blocks fibrinogen-dependant “outside-in” signaling through the integrin, this observation is most consistent with a defect in integrin-mediated secondary signaling in platelets from the affected horses. Biochemical analysis of Akt as well as mTOR and PDK1, which are immediately upstream to Akt in the signaling pathway, suggest that these enzymes are capable of normal function, leading us to investigate the role phosphatidylinositol 3-kinases in abnormal platelet function in the affected horses.

## Caroline Piskun

### Patient-derived tumor xenograft model of triple negative breast cancer suggests sensitivity to mTOR inhibitors

Piskun CM<sup>1</sup>, Zhang H<sup>1</sup>, Bild AH<sup>2</sup>, Jeffrey SS<sup>1</sup>

<sup>1</sup>Division of Surgical Oncology, Stanford University School of Medicine, Stanford, CA

<sup>2</sup>Department of Pharmacology & Toxicology, University of Utah, Salt Lake City, UT

**Background:** Breast cancer is the most common cancer in American women and a leading cause of female cancer death<sup>1</sup>. Triple negative breast cancer (TNBC), defined as estrogen and progesterone receptor-negative and HER2-negative, is a biologically aggressive subtype. It generally develops in younger women, carries a poor prognosis, and there is no currently available targeted therapy<sup>2</sup>. The PI3K-AKT- mTOR pathway is oncogenic and implicated in many cancers<sup>3</sup>. Drugs targeting this pathway, such as mTOR inhibitors and analogues, are under Phase I/II clinical investigation. Cell lines and subcutaneous mouse xenograft models have poor predictive value of human drug response<sup>4</sup>; thus, there are few preclinical models for accurately testing human drug response. Our laboratory has generated TNBC orthotopic xenograft models from patient biopsies for new drug testing.

**Materials and Methods:** Primary or metastatic TNBC tumors were minced and implanted into the mammary fat pads of NOD-SCID mice. After tumor development, the tumor was excised, the cells dissociated, and 1-3 x 10<sup>6</sup> cells were injected into 32 mice. After tumors reached 5mm, mice were randomly divided into four treatment groups: vehicle control; doxorubicin (standard breast cancer chemotherapy); rapamycin; and CCI-779 (rapamycin analogue). In another group of 32 mice, tumors were grown to 10mm then similarly treated. Tumors were measured twice weekly.

**Results:** Preliminary results show inhibition of primary TNBC growth by Rapamycin or CCI-779. Further studies of primary and metastatic TNBC are ongoing and will be presented.

**Conclusion:** Our data suggest that mTOR inhibition may be a viable therapeutic option in the treatment of TNBC.

## Ashley Talley

### Mesangial Cell-Derived Mfg-E8 Regulates Murine Glomerular Structure and Function

Ashley Talley, Mark C. Udey, and Sei-ichiro Motegi

Dermatology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20892-10908

MFG-E8 (a milk fat globule-associated protein with EGF- and Factor VIII-like domains) is a secreted protein that is produced by various cells, has multiple ligands and has been implicated in multiple functions and diseases. Recent work from our group demonstrated that vascular pericytes produce large amounts of MFG-E8, thus promoting angiogenesis *in vivo*. Since renal mesangial cells (MC) represent pericytes that are associated with glomerular capillary tufts, we hypothesized that MC might produce MFG-E8, and that this might have functional consequences. Multi-color immunofluorescence microscopy revealed intense MFG-E8 staining in murine glomeruli. Subsequent studies indicated that MFG-E8 co-localized with PDGFR $\beta$ <sup>+</sup> MC, rather than CD31<sup>+</sup> endothelial cells or podoplanin<sup>+</sup> podocytes. To determine if MC production of MFG-E8 was physiologically relevant, we screened MFG-E8 knockout and control mice for proteinuria. MFG-E8 knockout mice developed proteinuria

as early as 3 weeks after birth, and the incidence of proteinuria appeared to increase with age. At necropsy, MFG-E8 knockout kidneys were enlarged, were 20% heavier and were apparently hyperemic. More detailed microscopic studies indicated that renal vessels were less prominent (as assessed by extent of CD31 staining) and expression of podoplanin and synaptosin was also decreased. These results suggest that MC-derived MFG-E8 plays a role in development and/or maintenance of the glomerular filtration barrier, exerting significant effects on endothelial cells and podocytes (epithelial cells). Ongoing studies involving electron and confocal laser microscopy, in addition to other approaches, are intended to additionally characterize this phenotype and to elucidate the mechanism by which MFG-E8 acts.

## Lei Wang

### **Differentiation Of Aorta-Derived Mesoangioblasts Into The Oligodendrocyte Lineage Via Inhibition Of The Rho-Kinase (Rock) Signaling Pathway**

Lei Wang<sup>1</sup>, Anant Kamath<sup>2</sup>, Janie Frye<sup>3</sup>, Gary A. Iwamoto<sup>1</sup>, and Suzanne E. Berry<sup>1</sup>

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Mesoangioblasts are vessel-derived stem cells that differentiate into mesodermal derivatives, including smooth, skeletal and cardiac muscle cells, and adipocytes. We isolated mesoangioblasts from postnatal aorta (ADM) that regenerate damaged skeletal muscle in a murine model of Duchenne muscular dystrophy. In addition, ADM localize to peripheral nerve bundles in these muscles, and exhibit Schwann cell morphology, indicating that the cells give rise to myelinating glial cells in this regenerative environment. *In vitro* studies also support the potential of ADM to differentiate into myelinating glial cells. Inhibition of Rho kinase (ROCK) is essential for process extension in neural progenitor cells and oligodendrocytes from the CNS, and in ADM. ADMs cultured with Fasudil develop primary, secondary and tertiary branching characteristic of oligodendrocytes. In addition, ROCK inhibition also promotes an increase in ADM expression of the oligodendrocyte progenitor (OP) markers PDGFR1, A2B5, NG2 and the mid-to-late marker O4. Thyroid hormone is also important for oligodendrocyte maturation of ADM. ADM express the nuclear receptor for thyroid hormone, and enhanced branching complexity is observed when the active form of the hormone, L-3,5,3'-triiodothyronine (T3) is added to the medium. ADM injected into the lateral ventricle of the brain, migrate to the corpus callosum and cerebellar white matter, where they no longer express NG2, but are O4+ and GalC+, indicative of mature oligodendrocytes, components of myelin. We are therefore studying the Rho kinase pathway in ADM differentiation and whether ADM formation of myelinating glial cells can be utilized for treatment of demyelinating conditions as well as neuromuscular diseases.

## Age and Fasting Blood Glucose in Rhesus Macaques with Type II Diabetes is Associated with Changes in Size of Islets and Proportion of Islets Producing Insulin

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**Background:** The growing number of individuals with type II diabetes mellitus represents an unprecedented public health challenge. Animal models for type II diabetes mellitus are especially important in the context of the rising number of cases in man. Rhesus macaques (*Macaca mulatta*) are commonly used to explore the pathogenesis and clinical manifestations of type II diabetes mellitus. Although studies have been conducted using non human primates to model this disease, early morphologic changes in the pancreatic islets remain poorly defined.

**Methods:** Immunohistochemical staining techniques and spectral bright-field quantitative image analysis were used to measure the size of islets and relative proportion of islets stained for insulin in 24 rhesus macaques of two different age groups (Mean age: Juvenile = 4 yrs old, Adults = 17 yrs old).

**Results:** Size of islets ( $p < 0.03$ ), relative proportion of islets stained for insulin ( $p < 0.03$ ) and insulin area per islet ( $p < 0.005$ ) were larger in adults compared to those of juvenile animals. In fasted normoglycemic adult animals baseline glucose concentrations were positively correlated with relative proportion of islets stained for insulin ( $p < 0.01$ ,  $r = 0.78$ ) and percentage of islets of less than  $5,000 \mu\text{m}^2$  ( $p < 0.05$ ,  $r = 0.62$ ). In contrast blood glucose values were inversely correlated with the percentage of islets greater than  $10,000 \mu\text{m}^2$  ( $p < 0.03$ ,  $r = -0.80$ ).

**Conclusions:** These findings suggest that alterations in islet size may represent a more effective compensatory mechanism for controlling fasting blood glucose levels than changes in relative proportion of islet cells immunoreactive for insulin. Understanding the underlying mechanisms and transitions that occur during the early stages of type II diabetes may provide greater insight into the pathogenesis of the disease.

# **Symposium Participants**



# **Comparative Biomedical Scientist Training Program Symposium**

*Natcher Conference Center, Bethesda, Maryland  
September 8–10, 2010*

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NIH Comparative Biomedical Scientists  
Training Program Symposium  
September 8–10, 2010

National Cancer Institute