Pathology and Laboratory Medicine

Division Photo

Seated: Paul Steele MD, David Witte MD, Kevin Bove MD; Standing: Kathryn Wikenheiser-Brokamp MD PhD, Jerzy Stanek MD, Peter Tang PhD, Margaret Collins MD, Todd Boyd MD, Richard McMasters MD, Michael Miles PharmD, Julie Yin MD, Lili Miles MD, Joel Mortensen PhD, Jun Mo MD; Absent: Anita Gupta MD, Keith Stringer MD.

Division Data Summary

Research and Training Details	
Number of Faculty	17
Direct Annual Grant Support	$844,671
Direct Annual Industry Support	$105,510
Peer Reviewed Publications	28
Clinical Activities and Training	
Number of Clinical Fellows	2
Inpatient Encounters	1.2M
Outpatient Encounters	1.0M

Division Collaboration

Collaboration with Gastroenterology, Hepatology and Nutrition

Collaborating Faculty: Mitch Cohen MD; Jorge Bezerra MD; Xiaonan Han PhD; Noah Shroyer PhD

DigestiveHealthCenter. Integrated morphology core lab, provides technical and professional support to members of the DHC involved in basic and translational research in gastrointestinal tract .

Collaboration with Gastroenterology, Hepatology and Nutrition

Collaborating Faculty: James Heubi MD; John Bucuvalas MD; Jorge Bezerra MD; Kathleen Campbell MD

Director of Pathology Core for multicenter BARC and CLIC studies on biliary atresia and other chronic liver disorders in children.

Collaboration with Division of Immunobiology

Collaborating Faculty: Marsha Wills-Karp PhD; Fred FInkelman PhD

Morphology core lab, provides technical and professional support for PPG focused on IL13.

Collaboration with Division of Allergy and Immunology

Collaborating Faculty: Marc Rothenberg MD; Pablo Abonia Md

Providing professional support for the CincinnatiCenter for Eosinophilic Disorders program and related research.

Collaboration with Division of Hematology/Oncology

Collaborating Faculty: Maryam Fouladi MD; Richard Drissi PhD

Providing pathology professional and technical support for mutlicenter referral service for the High Grade Glioma program and basic research program.

Collaboration with Division of Heme/Onc Research

Collaborating Faculty: Yi Zheng Ph.D.; James Mulloy PhD; Jose Cancelas MD, PhD

Joint development of Leukemia Biology program at CCHMC.

Collaboration with Department of Surgery and Division of Heme/Onc

Collaborating Faculty: Denise Adams MD; Richard Azizkhan MD; Anusua Dasgupta MD

Hemangioma/Vascular malformation clinical program. Providing professional diagnostic and technical pathology support for mutlidisciplenary patient care program.

Faculty Members

David Witte, MD, Professor ; *Division Director*

Kevin E Bove, MD, Professor

J. Todd Boyd, DO, Assistant Professor

Margaret H Collins, MD, Professor

Anita Gupta, MD, Assistant Professor

Richard L McMasters, MD, Assistant Professor

Lili Miles, MD, Associate Professor

Michael Miles, PharmD, Professor Clinical

Jun Q Mo, MD, Assistant Professor

Joel E Mortensen, PhD, Associate Professor

Kenneth D Setchell, PhD, Professor

Jerzy W Stanek, MD, Professor

Paul E Steele, MD, Associate Professor

Keith F Stringer, MD, Assistant Professor

Peter Tang, PhD, Assistant Professor

Kathryn Wikenheiser-Brokamp, MD, Assistant Professor

Hong Yin, MD, Assistant Professor

Trainees

- **Rachel Sheridan, MD,** PGY-V, University of Cincinnati
- **Md Khalequzzaman, MD,** PGY-V, Howard University Hospital

Significant Accomplishments

Combined Programs

CCHMC is a nationally recognized center for diagnostic evaluation and management of children with severe liver disease. The Division of Gastroenterology and Nutrition has a strong clinical program that requires a multidisciplinary approach to evaluation and treatment of these patients. Pathology and Laboratory Medicine is an active member of this program both in clinical management and research programs contributing to the understanding of pediatric liver disease. Expertise and unique diagnostic lab services is provided by the Mass Spectrometry core facility of Dr. Setchell and the anatomic path service has a longstanding collaborative relationship with the GI service and Dr. Setchell in supporting the Liver Center. CCHMC was a participant in two NIH funded multicenter pediatric liver disease programs: the Biliary Atresia Research Consortium and Cholestatic Liver Disease Consortium, committed to providing centralized resources for collecting and making available specimens for research studies on pediatric liver diseases. Dr. Kevin Bove is chair of the Pathology core for both consortiums and the histopath core lab is based here. Funding for these programs was renewed

for 5 years during the past year but now as one consolidated multi-institutional program. In the past year the program has accessioned over 500 liver specimens nationally for ongoing research studies. Pediatric GI/liver disease research is also supported through Pathology and Laboratory Medicine as part of the Digestive Health Center, an NIH funded center supporting a large multidisciplinary group of investigators focused on the study of pediatric GI and liver diseases under the direction of Drs. Cohen and Bezerra (GI Division). The Integrative Morphology Core Lab provides comprehensive morphologic based technical support and expertise based in the Div of Pathology under the direction of Dr. Witte. These combined programs and divisional resources support a highly focused center of expertise in pediatric liver disease at CCHMC.

Pleuropulmonary Blastoma (PPB)

Pleuropulmonary blastoma (PPB) is a pediatric lung sarcoma that arises during fetal development. PPB is characterized by epithelial lined cysts and uncommitted mesenchymal cells that eventually overgrow the cysts to form solid high grade sarcomas. PPB is part of an inherited cancer syndrome and therefore the molecular events predisposing to PPB are likely relevant to other pediatric malignancies. Dr. Katherine Wikenheiser-Brokamp (Pathology) and her colleague Dr. Ashley Hill MD (Children's National Medical Center, Washington DC) identified germline loss of function *DICER1* mutations in ten PPB families. Preliminary data demonstrate that DICER1 protein is specifically lost in the PPB associated epithelium but not in the malignant mesenchymal component. They propose to generate a conditional *DICER1* deficient mouse model and to identify the developmental stages wherein DICER1 function is required. These studies will elucidate the role of DICER1 in lung development, and result in a clinically relevant, manipulatable model critical for elucidating molecular events underlying PPB pathogenesis.

Oncology Hematology Care (OHC) Contract/Clinical Lab LIS Upgrade

During the past year CCHMC has contracted with Oncology Hematology Care (OHC) to provide all the lab support for their clinical office practice. OHC is a group of 20 medical offices, providing most of the adult oncology services in the Greater Cincinnati Area, with more than 250,000 patient encounters a year. It represents a joint venture involving the Division of Pathology and Lab Med, Hematology Oncology, and Human Genetics. A centralized but separate processing facility has been established at the Oak campus to process a projected 250,000 samples per year from this large practice group. During the past year, the Clinical Lab has also totally rebuilt and upgraded its Laboratory Informatic System. The Cerner Millennium system has replaced the previous system which had been in use for the past 21 years. This system offers not only better speed and efficiency in work flow, but also will support many new capabilities not previously available to the CCHMC. This will include a new advanced system for detailed reporting on line of genetic tests, cytogenetics, and flow cytometry testing, as well as on line documentation of procedural steps to support each of those areas, reducing paper documentation. It will also provide new tools for more real time monitoring of workflow, QA, and turnaround times. More and improved management reports emanate from this system, including review queues for lab results that need supervisory and director-level sign-off or scrutiny. Bar coded processing of samples is also being implemented to improve efficiency and patient safety. Autoverification and enhanced use of rules is planned for this system. This system will provide better access to clinical data for clinical studies. Other changes in the clinical lab include renovation of the processing area to further enhance Lean Process changes, addition of a second Ortho Vitros Fusion chemistry analyzer, to provide a mirror backup instrument for the highest volume analyzer in the lab.

Division Publications

1. Kim HK, Goske MJ, Bove KE, Minovich E. **Segmental testicular infarction in a young man simulating a testicular tumor**. *Pediatr Radiol.* 2009; 39: 400-2.
2. Messina M, Watanabe S, Setchell KD. **Report on the 8th International Symposium on the Role of Soy in Health Promotion and Chronic Disease Prevention and Treatment**. *J Nutr.* 2009; 139: 796S-802S.
3. Zahedi K, Lentsch AB, Okaya T, Barone S, Sakai N, Witte DP, Arend LJ, Alhonen L, Jell J, Janne J, Porter CW, Soleimani M. **Spermidine/spermine-N1-acetyltransferase ablation protects against liver and kidney ischemia-reperfusion injury in mice**. *Am J Physiol Gastrointest Liver Physiol.* 2009; 296: G899-909.
4. Collins MH. **Histopathology associated with eosinophilic gastrointestinal diseases**. *Immunol Allergy Clin North Am.* 2009; 29: 109-17, x-xi.
5. Pentiuk S, Putnam PE, Collins MH, Rothenberg ME. **Dissociation between symptoms and histological severity in pediatric eosinophilic esophagitis**. *J Pediatr Gastroenterol Nutr.* 2009; 48: 152-60.
6. Steinberg SJ, Snowden A, Braverman NE, Chen L, Watkins PA, Clayton PT, Setchell KD, Heubi JE, Raymond GV, Moser AB, Moser HW. **A PEX10 defect in a patient with no detectable defect in peroxisome assembly or metabolism in cultured fibroblasts**. *J Inherit Metab Dis.* 2009; 32: 109-19.
7. Hoskins EE, Morris TA, Higginbotham JM, Spardy N, Cha E, Kelly P, Williams DA, Wikenheiser-Brokamp KA, Duensing S, Wells SI. **Fanconi anemia deficiency stimulates HPV-associated hyperplastic growth in organotypic epithelial raft culture**. *Oncogene.* 2009; 28: 674-85.
8. Gleason CE, Carlsson CM, Barnet JH, Meade SA, Setchell KD, Atwood CS, Johnson SC, Ries ML, Asthana S. **A preliminary study of the safety, feasibility and cognitive efficacy of soy isoflavone supplements in older men and women**. *Age Ageing.* 2009; 38: 86-93.
9. Loepke AW, Istaphanous GK, McAuliffe JJ, 3rd, Miles L, Hughes EA, McCann JC, Harlow KE, Kurth CD, Williams

MT, Vorhees CV, Danzer SC. The effects of neonatal isoflurane exposure in mice on brain cell viability, adult behavior, learning, and memory. *Anesth Analg.* 2009; 108: 90-104.

10. Wise-Draper TM, Morreale RJ, Morris TA, Mintz-Cole RA, Hoskins EE, Balsitis SJ, Husseinzadeh N, Witte DP, Wikenheiser-Brokamp KA, Lambert PF, Wells SI. DEK proto-oncogene expression interferes with the normal epithelial differentiation program. *Am J Pathol.* 2009; 174: 71-81.
11. Mullins ES, Kombrinck KW, Talmage KE, Shaw MA, Witte DP, Ullman JM, Degen SJ, Sun W, Flick MJ, Degen JL. Genetic elimination of prothrombin in adult mice is not compatible with survival and results in spontaneous hemorrhagic events in both heart and brain. *Blood.* 2009; 113: 696-704.
12. Zarate YA, Pacheco MC, Bove KE, Gorlin R, Zhao H, Hopkin RJ. Phenotypic and microscopic description of a new case of Ermine phenotype. *Am J Med Genet A.* 2009; 149A: 1253-6.
13. Bhatt A, Broxson E, Witte D, Omoloja A. Thrombocytopenia and proteinuria. Nonmuscle myosin heavy-chain-9-related disease (MYH9 RD) or Epstein syndrome (ES). *Pediatr Nephrol.* 2009; 24: 485-8.
14. West B, Bove KE, Slavotinek AM. Two novel STRA6 mutations in a patient with anophthalmia and diaphragmatic eventration. *Am J Med Genet A.* 2009; 149A: 539-42.
15. Wise-Draper TM, Mintz-Cole RA, Morris TA, Simpson DS, Wikenheiser-Brokamp KA, Currier MA, Cripe TP, Grosveld GC, Wells SI. Overexpression of the cellular DEK protein promotes epithelial transformation in vitro and in vivo. *Cancer Res.* 2009; 69: 1792-9.
16. Legg RL, Tolman JR, Lovinger CT, Lephart ED, Setchell KD, Christensen MJ. Diets high in selenium and isoflavones decrease androgen-regulated gene expression in healthy rat dorsolateral prostate. *Reprod Biol Endocrinol.* 2008; 6: 57.
17. Sun Y, Jia L, Williams MT, Zamzow M, Ran H, Quinn B, Aronow BJ, Vorhees CV, Witte DP, Grabowski GA. Temporal gene expression profiling reveals CEBPD as a candidate regulator of brain disease in prosaposin deficient mice. *BMC Neurosci.* 2008; 9: 76.
18. Tolman JR, Lephart ED, Setchell KD, Eggett DL, Christensen MJ. Timing of supplementation of selenium and isoflavones determines prostate cancer risk factor reduction in rats. *Nutr Metab (Lond).* 2008; 5: 31.
19. Sundaram SS, Bove KE, Lovell MA, Sokol RJ. Mechanisms of disease: Inborn errors of bile acid synthesis. *Nat Clin Pract Gastroenterol Hepatol.* 2008; 5: 456-68.
20. Sun Y, Witte DP, Ran H, Zamzow M, Barnes S, Cheng H, Han X, Williams MT, Skelton MR, Vorhees CV, Grabowski GA. Neurological deficits and glycosphingolipid accumulation in saposin B deficient mice. *Hum Mol Genet.* 2008; 17: 2345-56.
21. Frankenberg T, Miloh T, Chen FY, Ananthanarayanan M, Sun AQ, Balasubramaniyan N, Arias I, Setchell KD, Suchy FJ, Shneider BL. The membrane protein ATPase class I type 8B member 1 signals through protein kinase C zeta to activate the farnesoid X receptor. *Hepatology.* 2008; 48: 1896-905.
22. Miles MV, Tang PH, Miles L, Steele PE, Moye MJ, Horn PS. Validation and application of an HPLC-EC method for analysis of coenzyme Q10 in blood platelets. *Biomed Chromatogr.* 2008; 22: 1403-8.
23. Baboiu OE, Saal H, Collins M. Hepatic mesenchymal hamartoma: cytogenetic analysis of a case and review of the literature. *Pediatr Dev Pathol.* 2008; 11: 295-9.
24. Pacheco MC, Bove KE. Variability of acetylcholinesterase hyperinnervation patterns in distal rectal suction biopsy specimens in Hirschsprung disease. *Pediatr Dev Pathol.* 2008; 11: 274-82.
25. Sharma V, Crawford AH, Evans J, Collins MH. Sequential Ewing's sarcoma and osteosarcoma. *J Pediatr Orthop B.* 2008; 17: 333-7.
26. Ahrens R, Waddell A, Seidu L, Blanchard C, Carey R, Forbes E, Lampinen M, Wilson T, Cohen E, Stringer K, Ballard E, Munitz A, Xu H, Lee N, Lee JJ, Rothenberg ME, Denson L, Hogan SP. Intestinal macrophage/epithelial cell-derived CCL11/eotaxin-1 mediates eosinophil recruitment and function in pediatric ulcerative colitis. *J Immunol.* 2008; 181: 7390-9.
27. Kessler CA, Bachurski CJ, Schroeder J, Stanek J, Handwerger S. TEAD1 inhibits prolactin gene expression in cultured human uterine decidual cells. *Mol Cell Endocrinol.* 2008; 295: 32-8.
28. Chhabra MS, Motley WW, 3rd, Mortensen JE. Eikenella corrodens as a causative agent for neonatal conjunctivitis. *J AAPOS.* 2008; 12: 524-5.

Grants, Contracts, and Industry Agreements

Grant and Contract Awards — Annual Direct / Project Period Direct

SETCHELL, K

Soy Isoflavone Metabolite Equol- Its Formation and Fate

National Institutes of Health
R01 AT 002190 09/30/05 - 07/31/09 $251,097 / $1,091,629

Rare Liver Disease Network
National Institutes of Health (The Children's Hospital of Denver)
U54 DK 078377 09/30/04 - 07/31/09 $152,119 / $377,891

WIKENHEISER-BROKAMP, K

Role of Rb Family in Lung Epithelial Responses to Injury
National Institutes of Health
R01 HL 079193 05/05/08 - 01/31/10 $237,045 / $737,633

Role of Rb Family in Lung Epithelial Responses to Injury
National Institutes of Health
R01 HL 079193 06/01/09 - 08/31/10 $8,400 / $8,400

WITTE, D

Digestive Health Center: Bench to Bedside Research in Pediatric Digestive Disease
National Institutes of Health
P30 DK 078392 08/01/07 - 05/31/12 $113,119 / $113,119

Interleukin-13 in Experimental Asthma
National Institutes of Health
P01 HL 076383 07/01/04 - 06/30/09 $82,891 / $82,891

Industry Contracts

Miles
Tishcon Corporation $ 830

Mortensen
Microbiology Research $ 56,048

Witte
Ception Therapeutics Inc $ 48,605

Current Year Direct Receipts **$105,510**

Total $ 950,181