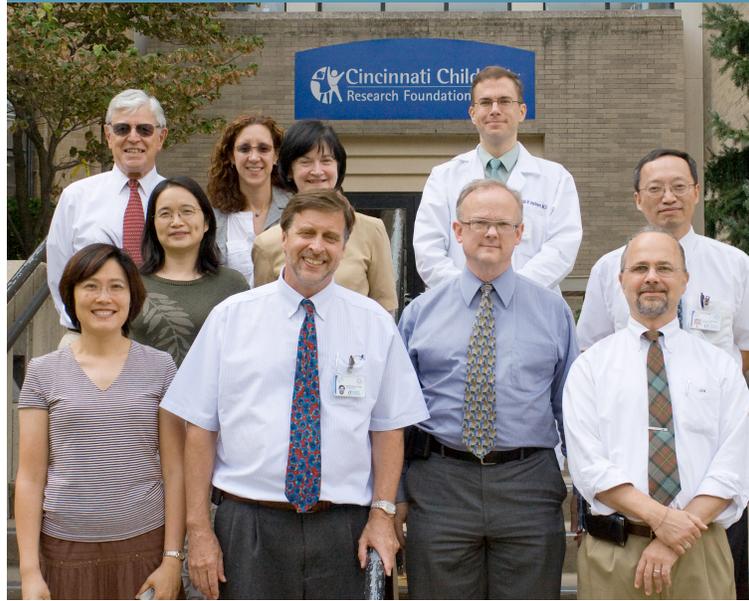


## Pathology and Laboratory Medicine

### Division Photo



**First Row:** L. Miles, D. Witte, P. Steele, J. Mortensen. **Second Row:** J. Mo, M. Collins, P. Tang. **Third Row:** K. Bove, G. Deutsch, K. Stringer

### Division Data Summary

#### Research and Training Details

Number of Faculty	16
Direct Annual Grant Support	\$1,279,829
Direct Annual Industry Support	\$28,606
Peer Reviewed Publications	41

#### Clinical Activities and Training

Number of Clinical Fellows	2
Inpatient Encounters	1,124,841
Outpatient Encounters	1,009,506

### Faculty Members

**David Witte, MD**, Professor ; *Division Director*

**Kevin E Bove, MD**, Professor

**Margaret H Collins, MD**, Professor

**Gail H Deutsch, MD**, Assistant Professor

**Anita Gupta, MD**, Assistant Professor

**Richard L McMasters, MD**, Assistant Professor

**Lili Miles, MD**, Assistant Professor

**Michael Miles, PharmD**, Professor Clinical

**Jun Q Mo, MD**, Assistant Professor

**Joel E Mortensen, PhD**, Associate Professor

**Kenneth D Setchell, PhD**, 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

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- **J Todd Boyd, DO**, PGY-VI, University of Cincinnati
- **Zhongxin Yu, MD**, PGY-VI, University of Oklahoma

## Significant Accomplishments in FY08

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### Equol Production in the Human Infant

Equol is a nonsteroidal estrogen, which is considered the most important metabolite of ingested soy isoflavones. It is made by intestinal bacteria and is not found in the urine and blood of infants before four months of age. For unknown reasons, only one-third of adults consuming soy foods make equol. Recent studies of osteoporosis prevention, cardiovascular health, and menopause have shown that beneficial effects from soy foods are significantly greater in people who are equol producers compared with those unable to make equol. Since there are advantages to being an equol producer, it is important to understand the factors governing equol production. This study was performed to determine when equol first appears in early life and whether it is differences in the type of early infant nutrition or the composition of the post weaning diet that predisposes to the production of equol. Given the clinical relevance of equol, a greater understanding of factors governing its production is essential. The results of this study will facilitate future strategies to manipulate equol production and enhance the overall clinical effectiveness of soy foods. Dr. Setchell's lab has been prospectively characterizing a study group of 90 babies and infants to determine at what age human infants become a producer of equol and what factors may contribute to this production. Dr. Setchell's current work is now determining at what time point human infants begin to produce equol and some preliminary results indicate it is likely to be earlier in development than has been previously recognized. Also related to his research work in the nutritional regulation of equol production, Dr. Setchell also has a second NIH funded study to determine the potential anti-tumor effects of equol when fed as a supplement. Dr. Setchell's lab is currently using a breast cancer model in laboratory animals to determine the potential beneficial effects of equol supplement to cancer protection. In his current studies it appears that some forms of equol have some protection in preventing either the development of breast cancer or possibly the progression of breast cancer in this animal model. This has potentially important therapeutic implications as equol could represent an important diet supplement in the prevention of some cancer developments. Dr. Setchell's work on equol has been recognized for its significance and potential impact on human health. The Japanese pharmaceutical company, Osaki, has recently performed a preliminary study to determine the pharmacokinetics of equol based on the equol product they have synthesized for potential dietary supplementation. In addition, Dr. Setchell has also been invited to give a plenary lecture at the Chinese National Nutrition Conference in Beijing in October, 2008.

### Multi-Institutional Studies on Pediatric Liver and GI Diseases

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 the evaluation and treatment of these patients. The Division of Pathology and Laboratory Medicine is an active member of this program both in clinical management and research programs that contribute to the understanding of pediatric liver disease. In addition to the expertise and unique diagnostic laboratory services provided by the Mass Spec core facility of Dr. Setchell, the Anatomic Pathology service has a longstanding collaborative relationship with the GI service and Dr. Setchell in supporting the liver center at CCHMC. There are two NIH funded multicenter pediatric liver disease programs which CCHMC is a participant: the BARC (Biliary Atresia Research Consortium) and CLIC (Cholestatic Liver Disease Consortium) which is committed to providing centralized resources for collecting and making available specimens for research studies on pediatric liver diseases. Dr. Kevin Bove is the chair of the pathology core for both of these consortiums and the histopathology core lab is based here at CCHMC. Pediatric GI and liver disease research is also supported through the Division of Pathology and Lab Medicine as a part of the Digestive Health Center (DHC). This is an NIH funded center which supports a large multidisciplinary group of investigators focused on the study of pediatric GI and liver diseases. The program is under the direction of Drs. Cohen and Bezerra (Division of Gastroenterology and

Nutrition). The Integrative Morphology Core lab which provides comprehensive morphologic based technical support and expertise based in the Division 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.

## **OHC Contract**

The Oncology/Hematology Care, Inc. represents a large adult oncology practice group covering the Greater Cincinnati Area, parts of Northern Kentucky and Southeast Indiana. This oncology practice provides the largest group of adult oncology clinical service support in this area with patient care provided at most of the adult community hospitals in this area including The Christ Hospital, The Jewish Hospital, University Hospital, and other large adult care providers in the Greater Cincinnati Area. As much of the care provided by this clinical practice group requires extensive clinical laboratory support, including both standard, routine laboratory testing as well as complex esoteric testing. During the past year, OHC has negotiated a contract with CCHMC to provide all the laboratory testing to support this large, adult oncology practice group. This contractual arrangement includes the laboratories of the Division of Pathology & Laboratory Medicine, Human Genetics, and the Division Hematology/Oncology. The combined laboratory services at CCHMC will provide full and comprehensive lab testing to this large practice group through a laboratory operation that has been customized to meet the unique needs for this adult oncology patient care service. This represents a new opportunity for the combined laboratory services here at CCHMC to fill a unique niche in the laboratory market here in the Greater Cincinnati Area. It is projected that more than 150,000 clinical laboratory tests will be performed per year for this practice group and the projected gross revenues over a five year period is approximately 98 million dollars. CCHMC welcomes the opportunity to partner with this large clinical care group in recognition of its strong reputation to provide comprehensive, high-quality laboratory services to the community.

## **Division Highlights**

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### **Digestive Health Center**

The integrative morphology core lab, which is based in the Division of Pathology at CCHMC, provides all the morphology and pathology support for the new Digestive Health Center (DHC) program at CCHMC. The integrative morphology core lab of the DHC will promote further development of the pre-existing morphology support within the Children's Hospital Research Foundation and the University of Cincinnati College of Medicine. It provides technical and analytical expertise to support and enhance a wide range of morphology based applications as they relate to the better understanding of gastrointestinal disorders of children and the development of the gastrointestinal tract. This core lab provides morphology support for a large number of members of the DHC at CCHMC. The core lab is under the direction of Dr. David Witte, and is supported by Dr. Keith Stringer as the staff pathologist. The core lab has a utilization rate by the DHC members and in the upcoming American Association for the Study of Liver Disease meeting, as well as the North American Society for Gastroenterology, Hepatology, and Nutrition/Children's Health and Nutrition Foundation meeting, there will be more than fifteen abstracts presented, many of which were supported by the core laboratory function.

### **Dr. Ken Setchell**

Dr. Ken Setchell's research program to characterize the metabolic production of equol continues to provide important new data and understanding of the bioproduction of equol in both adults and children. In recognition of Dr. Setchell's expertise in this area, he has been invited to give a plenary lecture at the Chinese National Nutrition Conference in Beijing in October, 2008.

### **Dr. Kevin Bove**

Dr. Kevin Bove is actively involved in two NIH funded, rare liver disorder, multicenter studies. These studies have focused on developing a better understanding of pediatric liver disorders such as biliary atresia, and a number of uncommon or rare cholestatic liver disorders in children, which frequently progress to chronic liver disease. This multi-institutional study has provided centralized specimen collections and protocols for evaluating liver biopsies in these patients. The pathology division at CCHMC is the core pathology facility for many of these studies.

### **Dr. Margaret Collins**

Dr. Margaret Collins is a co-investigator and a member of the Eosinophilic Diseases Center here at CCHMC. Dr. Collins continues to provide pathology support of the therapeutic clinical trials supported by the GlaxoSmithKline Company for the treatment of eosinophilic disorders of the gastrointestinal tract. These studies are performed in collaboration with the divisions of Allergy and Immunology, and Gastroenterology & Nutrition.

### **Dr. Kathryn Wikenheiser-Brokamp**

Dr. Wikenheiser-Brokamp currently has an NIH funded study to determine the role of the retinoblastoma gene family in

lung epithelial response to injury. The retinoblastoma gene and p16 tumor suppressors function in a common regulatory pathway that is universally deregulated in lung cancer. The central hypothesis of the studies being performed at Dr. Wikenheiser-Brokamp's laboratory is that p16 has retinoblastoma independent tumor suppressive functions and that the effects of p53 deregulation in retinoblastoma deficient cells are determined by the specific p53 genetic alteration. It is expected that the results of these studies will significantly advance the field of pulmonary biology by providing insight into the molecular pathways regulating epithelial cell proliferation, differentiation, and survival in vivo: processes important in neoplastic as well as non-neoplastic lung disease.

## Division Collaboration

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### Collaboration with Gastroenterology and Nutrition

**Collaborating Faculty: Dr. Mitchell Cohen; Dr. Jorge Bezerra**  
Digestive Health Center Program

### Collaboration with Gastroenterology and Nutrition

**Collaborating Faculty: Dr. Philip Putnman**  
Eosinophilic Esophagitis

### Collaboration with Division of Hematology/Oncology Research

**Collaborating Faculty: Dr. David Williams; Dr. Jose Cancelas**  
Characterization of gene regulation in myelopoiesis and erythropoiesis

### Collaboration with Division of Allergy & Immunology

**Collaborating Faculty: Dr. Marc Rothenberg**  
Characterization of gene regulation of eosinophilic esophagitis.

### Collaboration with Hematology/Oncology Research

**Collaborating Faculty: Dr. Nancy Ratner; Dr. Jose Cancelas; Dr. J. Wu**  
Characterization of NF1 gene loss in neurofibromas.

### Collaboration with Division of Rheumatology

**Collaborating Faculty: Dr. Daniel Lovell; Dr. Hermine Brunner**  
Retrospective study of the clinical course of juvenile dermatomyositis based on muscle biopsy

### Collaboration with Division of Neurology

**Collaborating Faculty: Dr. Ton DeGrauw; Dr. Brenda Wong**  
Systemic evaluation of muscle Coenzyme Q10 content with mitochondrial respiratory chain enzyme deficiencies

### Collaboration with Division of Hematology/Oncology; Division of Developmental Biology

**Collaborating Faculty: Dr. Clinton Joiner; Dr. Jay Degen**  
Role of fibrinogen deficiency increases mortality in SAD transgenic mice.

### Collaboration with Division of Gastroenterology & Nutrition

**Collaborating Faculty: Dr. Jorge Bezerra**  
Characterization of epithelial injury and autoimmunity in an experimental biliary atresia.

### Collaboration with Division of Bioinformatics

**Collaborating Faculty: Dr. Bruce Aronow**  
Characterization of retinoblastoma gene loss promotes liver tumor development.

### Collaboration with Division of Adolescent Medicine

**Collaborating Faculty: Dr. J. Huppert; Dr. J. Kahn**  
Myoplasma genitalium associated with Chlamydia trachomatis in adolescent women.

## Mentions in Consumer Media

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## Division Publications

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1. Blanchard C, Mingler MK, Vicario M, Abonia JP, Wu YY, Lu TX, Collins MH, Putnam PE, Wells SI, Rothenberg ME. [IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids](#). *J*

*Allergy Clin Immunol.* 2007; 120: 1292-300.

2. Boor I, Nagtegaal M, Kamphorst W, van der Valk P, Pronk JC, van Horssen J, Dinopoulos A, Bove KE, Pascual-Castroviejo I, Muntoni F, Estevez R, Scheper GC, van der Knaap MS. [MLC1 is associated with the dystrophin-glycoprotein complex at astrocytic endfeet](#). *Acta Neuropathol.* 2007; 114: 403-10.
3. Bullock JZ, Villanueva JM, Blanchard C, Filipovich AH, Putnam PE, Collins MH, Risma KA, Akers RM, Kirby CL, Buckmeier BK, Assa'ad AH, Hogan SP, Rothenberg ME. [Interplay of adaptive th2 immunity with eotaxin-3/c-C chemokine receptor 3 in eosinophilic esophagitis](#). *J Pediatr Gastroenterol Nutr.* 2007; 45: 22-31.
4. Castro DE, Wikenheiser-Brokamp KA, Sinha P. [A 56-year-old Honduran man with fever, weight loss and pleuritic chest pain](#). *Infect Dis Clin Pract.* 2008; 16: 36-40.
5. Clerici C, Setchell KD, Battezzati PM, Pirro M, Giuliano V, Asciutti S, Castellani D, Nardi E, Sabatino G, Orlandi S, Baldoni M, Morelli O, Mannarino E, Morelli A. [Pasta naturally enriched with isoflavone aglycons from soy germ reduces serum lipids and improves markers of cardiovascular risk](#). *J Nutr.* 2007; 137: 2270-8.
6. Collins MH. [Histopathologic features of eosinophilic esophagitis](#). *Gastrointest Endosc Clin N Am.* 2008; 18: 59-71; viii-ix.
7. Collins MH, Blanchard C, Abonia JP, Kirby C, Akers R, Wang N, Putnam PE, Jameson SC, Assa'ad AH, Konikoff MR, Stringer KF, Rothenberg ME. [Clinical, pathologic, and molecular characterization of familial eosinophilic esophagitis compared with sporadic cases](#). *Clin Gastroenterol Hepatol.* 2008; 6: 621-9.
8. Cristina Pacheco M, Miles L, Bove KE. [False negative histochemical reaction for myophosphorylase activity in fulminant sepsis due to methicillin resistant Staphylococcus aureus](#). *Neuromuscul Disord.* 2007; 17: 983-5.
9. Currier MA, Gillespie RA, Sawtell NM, Mahller YY, Stroup G, Collins MH, Kambara H, Chiocca EA, Cripe TP. [Efficacy and safety of the oncolytic herpes simplex virus rRp450 alone and combined with cyclophosphamide](#). *Mol Ther.* 2008; 16: 879-85.
10. DeBurger B, Mortensen J. [What's new in the world of swabs?](#). *J Contin Educ Topics Issues.* 2008; 10: 18-22.
11. Duran A, Linares JF, Galvez AS, Wikenheiser K, Flores JM, Diaz-Meco MT, Moscat J. [The signaling adaptor p62 is an important NF-kappaB mediator in tumorigenesis](#). *Cancer Cell.* 2008; 13: 343-54.
12. Flick MJ, LaJeunesse CM, Talmage KE, Witte DP, Palumbo JS, Pinkerton MD, Thornton S, Degen JL. [Fibrin\(ogen\) exacerbates inflammatory joint disease through a mechanism linked to the integrin alphaMbeta2 binding motif](#). *J Clin Invest.* 2007; 117: 3224-35.
13. Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, Bonis P, Hassall E, Straumann A, Rothenberg ME. [Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment](#). *Gastroenterology.* 2007; 133: 1342-63.
14. Geller JL, Argani P, Adeniran A, Hampton E, De Marzo A, Hicks J, Collins MH. [Translocation renal cell carcinoma: lack of negative impact due to lymph node spread](#). *Cancer.* 2008; 112: 1607-16.
15. Ghiaur G, Ferkowicz MJ, Milsom MD, Bailey J, Witte D, Cancelas JA, Yoder MC, Williams DA. [Rac1 is essential for intraembryonic hematopoiesis and for the initial seeding of fetal liver with definitive hematopoietic progenitor cells](#). *Blood.* 2008; 111: 3313-21.
16. Hecht N, Omoloja A, Witte D, Canessa L. [Evolution of antiglomerular basement membrane glomerulonephritis into membranous glomerulonephritis](#). *Pediatr Nephrol.* 2008; 23: 477-80.
17. Herring NR, Schaefer TL, Tang PH, Skelton MR, Lucot JP, Gudelsky GA, Vorhees CV, Williams MT. [Comparison of time-dependent effects of \(+\)-methamphetamine or forced swim on monoamines, corticosterone, glucose, creatine, and creatinine in rats](#). *BMC Neurosci.* 2008; 9: 49.
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19. Johansson G, Mahller YY, Collins MH, Kim MO, Nobukuni T, Perentesis J, Cripe TP, Lane HA, Kozma SC, Thomas G, Ratner N. [Effective in vivo targeting of the mammalian target of rapamycin pathway in malignant peripheral nerve sheath tumors](#). *Mol Cancer Ther.* 2008; 7: 1237-45.
20. Lee K, Liu Y, Mo JQ, Zhang J, Dong Z, Lu S. [Vav3 oncogene activates estrogen receptor and its overexpression may be involved in human breast cancer](#). *BMC Cancer.* 2008; 8: 158.
21. Ma L, Teruya-Feldstein J, Bonner P, Bernardi R, Franz DN, Witte D, Cordon-Cardo C, Pandolfi PP. [Identification of S664 TSC2 phosphorylation as a marker for extracellular signal-regulated kinase mediated mTOR activation in tuberous sclerosis and human cancer](#). *Cancer Res.* 2007; 67: 7106-12.
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- GP, Lee JS, Aronow BJ, Thorgeirsson SS, Knudsen ES. [RB loss abrogates cell cycle control and genome integrity to promote liver tumorigenesis](#). *Gastroenterology*. 2007; 133: 976-84.
24. McKenney JK, Collins MH, Carretero AP, Boyd TK, Redman JF, Parham DM. [Penile myointimoma in children and adolescents: a clinicopathologic study of 5 cases supporting a distinct entity](#). *Am J Surg Pathol*. 2007; 31: 1622-6.
25. Miles L, Bove KE, Lovell D, Wargula JC, Bukulmez H, Shao M, Salisbury S, Bean JA. [Predictability of the clinical course of juvenile dermatomyositis based on initial muscle biopsy: a retrospective study of 72 patients](#). *Arthritis Rheum*. 2007; 57: 1183-91.
26. Miles MV, Miles L, Tang PH, Horn PS, Steele PE, DeGrauw AJ, Wong BL, Bove KE. [Systematic evaluation of muscle coenzyme Q10 content in children with mitochondrial respiratory chain enzyme deficiencies](#). *Mitochondrion*. 2008; 8: 170-80.
27. Miles MV, Patterson BJ, Chalfonte-Evans ML, Horn PS, Hickey FJ, Schapiro MB, Steele PE, Tang PH, Hotze SL. [Coenzyme Q10 \(ubiquinol-10\) supplementation improves oxidative imbalance in children with trisomy 21](#). *Pediatr Neurol*. 2007; 37: 398-403.
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# Grants, Contracts, and Industry Agreements

## Grant and Contract Awards

Annual Direct / Project Period Direct

### Setchell, K

#### Rare Liver Disease Network

National Institutes of Health (The Children's Hospital of Denver)

U54 DK 078377 09/30/04 - 07/31/08

\$77,808 / \$225,772

#### Rare Liver Disease Network

National Institutes of Health (The Children's Hospital of Denver)

U54 DK 078377 08/01/07 - 07/31/08

\$13,423 / \$13,423

#### Chemopreventive Actions of Equol Enantiomers

National Institutes of Health

R01 AT 003313 09/30/05 - 08/31/08

\$205,126 / \$716,211

#### Soy Isoflavone Metabolite Equol- Its Formation And Fate

National Institutes of Health

R01 AT 002190 09/30/05 - 07/31/09

\$275,234 / \$1,091,629

### Wikenheiser-Brokamp, K

#### Role of Rb Family in Lung Epithelial Response to Injury

National Institutes of Health

R01 HL 079193 05/05/08 - 01/31/10

\$500,588 / \$737,633

### Witte, D

#### Digestive Health Center - Bench to Bedside Research in Pediatric Digestive Disease - Integrative Morphology Core

National Institutes of Health

P30 DK078391 08/01/07 - 05/31/12

\$111,861 / \$225,204

#### Interleukin-13 in Experimental Asthma

National Institutes of Health

P01 HL 076383 07/01/04 - 06/30/09

\$95,789 / \$543,205

**Current Year Direct**

**\$1,279,829**

## Industry Contracts

### Mortensen, J

Microbiology Research

\$ 28,606

**Current Year Direct Receipts**

**\$28,606**

**Total \$1,308,435**