Pathology

Division Details

RESEARCH AND TRAINING DETAILS	
Faculty	**22**
Total Annual Grant Award Dollars	**$644,551**

CLINICAL ACTIVITIES AND TRAINING	
Staff Physicians	**15**
Clinical Fellows	**2**
Inpatient Encounters	**80,718**
Outpatient Encounters	**138,472**

Row 1: J Stanek, S Szabo, R Sheridan, P Tang, E Martinez

Row 2: S Johnson, P Steele, K Wikenheiser-Brokamp, D Witte, L Romick-Rosendale, J Mortensen, M Azam

Row 3: C Fuller, K Bove, K Setchell, M Collins, R Lorsbach, M McCoy, S Kinney A Gupta

Visit Pathology and Laboratory Medicine

Division Highlights

Mass Spectrometry-NMR Lab

The Division of Pathology has been investing significantly towards the growth and development of a stronger metabolomics core service incorporating the expertise and resources of both the Mass Spectroscopy Facility, under the direction of Dr. Kenneth Setchell, PhD, and the nuclear magnetic resonance (NMR) service under the direction of Dr. Lindsay Romick-Rosendale, PhD. Metabolomics studies are highly complex, requiring sophisticated technology and resources to provide the Cincinnati Children's Hospital Medical Center investigators adequate technology for sensitive analysis and high throughput evaluation. The Mass Spectroscopy Facility has a longstanding, international recognized, successful track record for advancing the understanding of bile acid metabolism and characterizing the normal physiologic role bile acids play in the metabolism, as well as providing critical diagnostic testing for patients around the world with bile acid defects. This has now led to FDA approved clinical treatment of patients with these rare disorders as a result of decades of research involving Dr. Setchell in collaboration with Dr. James Heubi, MD, in the Division of Gastroenterology, Hepatology and Nutrition. Dr. Setchell continues his highly productive metabolomics core support including critical new scientific publications including the *Journal of Science Translational Medicine* on the impact of bile acid uptake on fatty liver disease, as well as other metabolic disorders including a recent publication in *Nature*, in collaboration with the Division of Human Genetics, on the underlying mechanism of tissue damage in Gaucher disease. Dr. Setchell's Mass Spectroscopy Facility core service also provided important data for a recent publication in *Nature*, in collaboration with the Division of Experimental Hematology research group on stem cell microenvironment changes in leukemia. The Mass Spectroscopy Facility service is also providing critical support and expertise in collaboration with the efforts of Dr. Scott Wexelblatt, MD, in the Division of Neonatology, to address the explosive opioid crisis in this county, and, in particular, its role in neonatal abstinence syndrome. The mass spectroscopy lab provides critical and rapid drug testing confirmation for newborns throughout the entire Greater

Cincinnati Area under the care of our neonatology group. In an effort to expand this service in the management and care of these newborns, Dr. Setchell and his group have developed new drug testing capabilities utilizing umbilical cord tissue, which will provide broader coverage in identifying affected newborns in a timely manner for our neonatologists confronted with the challenge on a daily basis in the newborn units. This type of testing, with the needed technical expertise and resources, is only available in a very limited number of labs throughout the country.

Dr. Romick-Rosendale has been a member of the Division of Pathology for the past few years, and is responsible for the establishment of the NMR lab as an additional resource for Cincinnati Children's investigators requiring full support in the metabolomics studies. During the past few years, Dr. Romick-Rosendale has provided analytical support based on NMR technology to a number investigators at Cincinnati Children's as well as other institutions, including the University of Cincinnati and the Cincinnati Zoo on metabolomics research. She provided critical analytical support to a large study directed by Dr. Louis Muglia, MD, PhD, in an effort to identify mother's at risk for premature labor based on metabolic profiles. She evaluated more than 3,000 samples for the study with the goal of developing a reliable method for identifying these at risk patients. NMR technology support is also providing analysis of bone marrow transplant patients in collaboration with Dr. Stella Davies, MBBS, PhD, MRCP, in an effort to recognize and monitor bone marrow transplant patients at risk for a graft versus host disease, a deadly complication associated with bone marrow transplantation. The Cincinnati Zoo is also working closely with this core lab to perform a number of metabolic studies on endangered animals to improve birth rates, to identify metabolic disease in endangered animals, and to identify the development of cancer in some of these populations. This lab evaluated more than 2,000 samples in the past few years as a result of this collaboration for metabolomic studies. The near future for the metabolomics program in the division includes an effort to establish a lipidomics program as the next frontier to complete metabolomics studies at Cincinnati Children's. This will involve both mass spectroscopy and NMR based analyses, which will complement each other in providing this cutting edge technology for the advancement of metabolomics studies at Cincinnati Children's.

Leukemia Research

Dr. Mohammad Azam, PhD, a member of the Division of Pathology faculty, has a well-established program jointly supported by the Divisions of Pathology and Experimental Hematology studying drug resistance in various forms of chronic myeloid leukemia. Published recent work in this area are in *Nature Medicine* and *Oncotarget*. Chronic myeloid leukemia treatment with BCR-ABL inhibitors is often limited by the development of drug resistance. Therefore, as in other forms of cancer, therapy for human cancers is frequently not curative, and relapse occurs due to the continued presence of tumor cells recognized as minimal residual disease, many of which appear to have an intrinsic resistance to some forms of therapy. Studies, that Dr. Azam recently collaborated with other investigators at Cincinnati Children's Hospital Medical Center, have shown one small molecule compound, Bisindolylmaleimide IX inhibits DNA topoisomerase, generates DNA breaks, and induced cell cycle arrest and cell death. These studies found that this drug is highly effective in targeting cells positive for the BCR-ABL mutation. Dr. Azams's other related studies have recently shown that an oncogene (FOS), and a dual specificity phosphatase 1 (DUSP1), could be deleted, which suppressed tumor growth in BCR-ABL forms of chronic myeloid leukemia. Pharmacological inhibition of these genes eradicated minimal residual disease in multiple in vivo models including mice transplanted with patient derived primary CML cells. These studies demonstrate that the expression levels of these genes may determine the threshold of resistance to therapy in these tumor cells in a wide range of leukemias, and might represent a unifying tool for treating kinase driven cancers.

Division Publications

1. Pandey MK; Burrow TA; Rani R; Martin LJ; Witte D; Setchell KD; Mckay MA; Magnusen AF; Zhang W; Liou B. **Complement drives glucosylceramide accumulation and tissue inflammation in Gaucher disease.** *Nature*. 2017; 543:108-112.

2. Dong L; Yu WM; Zheng H; Loh ML; Bunting ST; Pauly M; Huang G; Zhou M; Broxmeyer HE; Scadden DT. **Leukaemogenic effects of Ptpn11 activating mutations in the stem cell microenvironment.** *Nature*. 2016; 539:304-308.

3. Kesarwani M; Kincaid Z; Gomaa A; Huber E; Rohrabaugh S; Siddiqui Z; Bouso MF; Latif T; Xu M; Komurov K. **Targeting c-FOS and DUSP1 abrogates intrinsic resistance to tyrosine-kinase inhibitor therapy in BCR-ABL-induced leukemia.** *Nature Medicine*. 2017; 23:472-482.

4. Fang J; Bolanos LC; Choi K; Liu X; Christie S; Akunuru S; Kumar R; Wang D; Chen X; Greis KD. **Ubiquitination of hnRNPA1 by TRAF6 links chronic innate immune signaling with myelodysplasia.** *Nature Immunology*. 2017; 18:236-245.

5. Rosen MJ; Karns R; Vallance JE; Bezold R; Waddell A; Collins MH; Haberman Y; Minar P; Baldassano RN; Hyams JS. **Mucosal Expression of Type 2 and Type 17 Immune Response Genes Distinguishes Ulcerative Colitis From Colon-Only Crohn's Disease in Treatment-Naive Pediatric Patients.** *Gastroenterology*. 2017; 152:1345- 1357.e7.

6. Dellon ES; Katzka DA; Collins MH; Hamdani M; Gupta SK; Hirano I; MP-101-06 Investigators. **Budesonide Oral Suspension Improves Symptomatic, Endoscopic, and Histologic Parameters Compared With Placebo in Patients With Eosinophilic Esophagitis.** *Gastroenterology*. 2017; 152:776-786.e5.

7. Rao A; Kosters A; Mells JE; Zhang W; Setchell KDR; Amanso AM; Wynn GM; Xu T; Keller BT; Yin H. **Inhibition of ileal bile acid uptake protects against nonalcoholic fatty liver disease in high- fat diet-fed mice.** *Science Translational Medicine*. 2016; 8:357ra122-357ra122.

8. McCormack FX; Gupta N; Finlay GR; Young LR; Taveira-DaSilva AM; Glasgow CG; Steagall WK; Johnson SR; Sahn SA; Ryu JH. **Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guidelines: Lymphangioleiomyomatosis Diagnosis and Management.** *American journal of respiratory and critical care medicine*. 2016; 194:748- 761.

9. Lages CS; Simmons J; Maddox A; Jones K; Karns R; Sheridan R; Shanmukhappa SK; Mohanty S; Kofron M; Russo P. **The Dendritic Cell-T Helper 17-Macrophage Axis Controls Cholangiocyte Injury and Disease Progression in Murine and Human Biliary Atresia.** *Hepatology*. 2017; 65:174-188.

10. Link KA; Lin S; Shrestha M; Bowman M; Wunderlich M; Bloomfield CD; Huang G; Mulloy JC. **Supraphysiologic levels of the AML1-ETO isoform AE9a are essential for transformation.** *Proceedings of the National Academy of Sciences of the United States of America*. 2016; 113:9075-9080.

11. Nalapareddy K; Nattamai KJ; Kumar RS; Karns R; Wikenheiser-Brokamp KA; Sampson LL; Mahe MM; Sundaram N; Yacyshyn MB; Yacyshyn B. **Canonical Wnt Signaling Ameliorates Aging of Intestinal Stem Cells.** *Cell Reports*. 2017; 18:2608-2621.

12. Dellon ES; Collins MH; Bonis PA; Leung J; Capocelli KE; Dohil R; Falk GW; Furuta GT; Menard-Katcher C; Gupta SK. **Substantial Variability in Biopsy Practice Patterns Among Gastroenterologists for Suspected Eosinophilic Gastrointestinal Disorders.** *Clinical Gastroenterology and Hepatology*. 2016; 14:1842-1844.

13. Marahatta A; Megaraj V; McGann PT; Ware RE; Setchell KDR. **Stable-Isotope Dilution HPLC-Electrospray Ionization Tandem Mass Spectrometry Method for Quantifying Hydroxyurea in Dried Blood Samples.** *Clinical chemistry*. 2016; 62:1593-1601.

14. Liou B; Peng Y; Li R; Inskeep V; Zhang W; Quinn B; Dasgupta N; Blackwood R; Setchell KDR; Fleming S. **Modulating ryanodine receptors with dantrolene attenuates neuronopathic phenotype in Gaucher disease mice.** *Human Molecular Genetics*. 2016; 25:ddw322.

15. Himes RW; Barlow SE; Bove K; Quintanilla NM; Sheridan R; Kohli R. **Lysosomal Acid Lipase Deficiency Unmasked in Two Children With Nonalcoholic Fatty Liver Disease.** *Pediatrics*. 2016; 138:e20160214.

16. Wasserman H; Ikomi C; Hafberg ET; Miethke AG; Bove KE; Backeljauw PF. **Two Case Reports of FGF23-Induced Hypophosphatemia in Childhood Biliary Atresia.** *Pediatrics*. 2016; 138:e20154453.

17. Sen M; Akeno N; Reece A; Miller AL; Simpson DS; Wikenheiser-Brokamp KA. **p16 controls epithelial cell growth and suppresses carcinogenesis through mechanisms that do not require RB1 function.** *Oncogenesis*. 2017; 6:e320.

18. Koncar RF; Chu Z; Romick-Rosendale LE; Wells SI; Chan TA; Qi X; Bahassi EM. **PLK1 inhibition enhances temozolomide efficacy in IDH1 mutant gliomas.** *Oncotarget*. 2017; 8:15827-15837.

19. Wang J; Ai X; Qin T; Xu Z; Zhang Y; Liu J; Li B; Fang L; Zhang H; Pan L. **Multiplex ligation- dependent probe amplification assay identifies additional copy number changes compared with R-band karyotype and provide more accuracy prognostic information in myelodysplastic syndromes.** *Oncotarget*. 2017; 8:1603-1612.

20. Zhang X; Jia D; Ao J; Liu H; Zang Y; Azam M; Habib SL; Li J; Ruan X; Jia H. **Identification of Bisindolylmaleimide IX as a potential agent to treat drug-resistant BCR-ABL positive leukemia.** *Oncotarget*. 2016; 7:69945-69960.

21. Li B; Liu J; Qu S; Gale RP; Song Z; Xing R; Liu J; Ren Y; Xu Z; Qin T. **Colony-forming unit cell (CFU-C) assays at diagnosis: CFU-G/M cluster predicts overall survival in myelodysplastic syndrome patients independently of IPSS-R.** *Oncotarget*. 2016; 7:68023-68032.

22. Li B; Xu Z; Li Y; Peter Gale R; Song Z; Ai X; Qin T; Zhang Y; Zhang P; Huang G. **The different prognostic impact of type-1 or type-1 like and type-2 or type-2 like CALR mutations in patients with primary myelofibrosis.** *American Journal of Hematology*. 2016; 91:E320-E321.

23. Lobeck IN; Sheridan R; Lovell M; Dupree P; Tiao GM; Bove KE. **Cystic Biliary Atresia and Choledochal Cysts Are Distinct Histopathologic Entities.** *American Journal of Surgical Pathology*. 2017; 41:354-364.

24. Russo P; Magee JC; Anders RA; Bove KE; Chung C; Cummings OW; Finegold MJ; Finn LS; Kim GE; Lovell MA. **Key Histopathologic Features of Liver Biopsies That Distinguish Biliary Atresia From Other Causes of Infantile Cholestasis and Their Correlation With Outcome A Multicenter Study.** *American Journal of Surgical Pathology*. 2016; 40:1601-1615.

25. Stone AV; Little KJ; Glos DL; Stringer KF; Wall EJ. **Repetitive Stresses Generate Osteochondral Lesions in Skeletally Immature Rabbits.** *American Journal of Sports Medicine*. 2016; 44:2957-2966.

Grants, Contracts, and Industry Agreements

Annual Grant Award Dollars

Investigator	Title	Sponsor	ID	Dates	Amount
Gang Huang, PhD	Role of the Hypoxia-Inducible Factor-1alpha in Myelodysplastic Syndromes	National Institutes of Health	R01 DK105014	03/01/2015 - 02/29/2020	$351,000
Allie K Adams, PhD	Training Program in Cancer Therapeutics	National Institutes of Health (University of Cincinnati)	T32 CA117846	09/14/2015 - 09/13/2018	$43,551
Gang Huang, PhD	The Role of HIF-1α as a Central Pathobiologic Mediator of Myelodysplastic Syndromes	Taub Foundation Program for MDS Research	MDS	12/15/2016 - 12/14/2019	$200,000
Gang Huang, PhD	HIF-1α Signaling is a Central Pathobiologic Mediator of Hemophagocytic Lymphohistiocytosis	Histiocytosis Association of America	Huang, Gang, HAA	01/01/2017 - 12/31/2017	$50,000
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