

Critical Care Medicine



First Row: D. Wheeler, L. Doughty, B. Zingarelli; Second Row: K. Page, J. Kaplan, H. Wong, R. Chima, S. Poynter

Division Data Summary

Research and Training Details

Number of Faculty	11
Number of Support Personnel	22
Direct Annual Grant Support	\$1,081,863
Direct Annual Industry Support	\$6,747
Peer Reviewed Publications	31
Clinical Activities and Training	
Number of Clinical Follows	Ω

Number of Clinical Fellows 8 Inpatient Encounters 8,208

Faculty Members

Hector Wong, MD, Professor; Director

Research Interests: Heat shock protein biology

Eman Al-Khadra, MD, Research Instructor

Research Interests: Pleural effusion management
Richard Brilli, MD, Professor Clinical; Clinical Director
Research Interests: Quality Improvement BSI, VAP

Ranjit Chima, MD, Research Instructor

Research Interests: Lung Injury/Inflammation

Lesley Doughty, MD, Associate Professor Clinical; Fellowship Director

Research Interests: Sepsis

Jennifer Kaplan, MD, Research Instructor

Research Interests: Sepsis

Kristen Page, PhD, Research Assistant Professor

Research Interests: Asthma, airway inflammation

Sue E. Poynter, MD, Research Instructor; Medical Director Division of Respiratory Care

Research Interests: Surfactant biology

Kenneth Tegtmeyer, MD, Associate Professor Clinical Research Interests: Multimedia Medical Education

Derek S. Wheeler, MD, Assistant Professor Clinical; Associate Clinical Director

Research Interests: Stress preconditioning
Basilia Zingarelli, MD, Associate Professor
Research Interests: Myocardial infarction

Trainees

- o Jeffrey Nowak, , PL-8, University of Minnesota
- Erika Stalets, , PL-7, University of Tennessee Health Sciences Center
- Michael Bigham, , PL-6, Medical College of Ohio
- Scottie Day, , PL-6, Indiana University
- Elizabeth Galloway, , PL-6, University of South Dakota
- John Giuliano, , PL-6, George Washington School & Medicine and Health Safety
- Elizabeth Mack, , PL-5, Palmetto Richland University
- Ernest Lawhorn, , PL-4, Eastern Virginia Medical School

Significant Accomplishments in FY08

Thiazolidinediones and PPAR-g

Thiazolidinediones (TZDs) represent a class of FDA-approved drugs widely used in patients with type II diabetes. TZDs are pharmacologic ligands for the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-g). Ongoing work in the Division has identified PPAR-g as key negative modulator of inflammation and ischemic injury in animal models of myocardial ischemia, hemorrhagic shock, and sepsis. These data have demonstrated that activation of PPAR-g, through either genetic or pharmacologic manipulations, exerts cytoprotective effects in various tissues and organs. Thus, these data provide the foundation for the use of TZDs, or TZD-like drugs, in critically ill patients.

Translational studies in pediatric septic shock

Septic shock continues to be an important problem in the pediatric intensive care unit, carrying significant morbidity and mortality despite potent antibiotics and advanced modalities of organ support. The Division is the lead center for an ongoing, multi-institutional translational research program focused on pediatric septic shock. The core of the program is a genomic and clinical data bank representing over 300 children with septic shock from across the country. This databank is being mined to develop a more comprehensive biological understanding of clinical pediatric septic shock. The deliverables from the program thus far include the discovery of altered zinc homeostasis in children with septic shock, with concomitant profound alterations of the adaptive immune system. These types of data have served to generate novel hypotheses that can be brought back to the bench for formal testing. In addition, the database has provided the foundation for the development of biomarkers providing the ability to predict outcomes and responses to therapies.

Significant Publications in FY08

Page K, Lierl KM, Hughes VS, Zhou P, Ledford JR, and Wills-Karp M. 2008. TLR2-mediated activation of neutrophils in response to German cockroach frass. J Immunol 180:6317-6324.

Demonstration of key neutrophil signaling mechanisms by ubiquitous allergens associated with asthma.

Chima RS, Hake PW, Piraino G, Mangeshkar P, Denenberg A, and Zingarelli B. 2008. Ciglitazone ameliorates lung inflammation by modulating the inhibitor kappaB protein kinase/nuclear factor-kappaB pathway after hemorrhagic shock. Crit Care Med 36:2849-2857.

Preclinical work demonstrating efficacy of Thiazolidinediones in hemorrhagic shock

Wong HR, Cvijanovich N, Wheeler DS, Bigham MT, Monaco M, Odoms K, Macias WL, and Williams MD. 2008. Interleukin-8 as a stratification tool for interventional trials involving pediatric septic shock. Am J Respir Crit Care Med 178:276-282.

Foundation for the development of a feasible, robust biomarker for outcome in pediatric septic shock.

Division Collaboration

Collaboration with Immunobiology

Collaborating Faculty: Eman Al-Khadra; Kristen Page; Marsha Wills-Karp

Mentor

Mentions in Consumer Media

o Immune System Protein Accurate Predictor Of Survival In Pediatric Septic Shock Science Daily , Magazine

Division Publications

- 1. Bigham MT, Brady PW, Manning PB, Jacobs BR, Kimball TR, Wong HR. <u>Therapeutic application of intrapericardial tissue plasminogen activator in a 4-month-old child with complex fibropurulent pericarditis</u>. *Pediatr Crit Care Med.* 2008; 9: e1-4.
- 2. Bigham MT, Brilli RJ. **"Status Asthmaticus."** In: DG Nichols, MC Rogers, eds. *Rogers' textbook of pediatric intensive care.* Philadelphia: Lippincott Williams & Wilkins; 2008: 181-187.
- 3. Chase M, Brilli RJ. Reduction of catheter-associated bloodstream infections--child's play?. Pediatr Crit Care Med. 2008; 9: 119-20.
- 4. Mack EH, Brilli RJ. To err is human; to improve, divine. Pediatr Crit Care Med. 2007; 8: 398-9.
- 5. Nowak JE, Brilli RJ. Pediatric rapid response teams: is it time?. JAMA. 2007; 298: 2311-2.
- 6. Chima RS, Zingarelli B. Surfactant treatment of neonatal acute respiratory distress syndrome: is "fortification" the answer?. Crit Care Med. 2007; 35: 2442-3.
- 7. Zhao B, Sun L, Haas M, Denenberg AG, Wong HR, Shanley TP. PP2A regulates upstream members of the c-jun N-terminal kinase mitogen-activated protein kinase signaling pathway. Shock. 2008; 29: 181-8.
- 8. Chung CS, Chen Y, Grutkoski PS, Doughty L, Ayala A. <u>SOCS-1 is a central mediator of steroid-increased thymocyte apoptosis and decreased survival following sepsis</u>. *Apoptosis*. 2007; 12: 1143-53.
- 9. Doughty LA. **"The immune system and viral illness in the critically ill."** In: DG Nichols, MC Rogers, eds. *Rogers' textbook of pediatric intensive care.* Philadelphia: Lippincott Williams & Wilkins; 2008: 450-454.
- 10. Doughty LA. "The immune system and viral illness in the critically ill." Roger's textbook of pediatric intensive care. 2008:
- 11. Venkatakrishnan CD, Dunsmore K, Wong H, Roy S, Sen CK, Wani A, Zweier JL, Ilangovan G. <u>HSP27 regulates p53</u> transcriptional activity in doxorubicin-treated fibroblasts and cardiac H9c2 cells: p21 upregulation and G2/M phase cell cycle arrest. *Am J Physiol Heart Circ Physiol.* 2008; 294: H1736-44.
- 12. Galloway E, Doughty LA. Electrolyte emergencies and acute renal failure in pediatric critical care. Clin Pediatr Emerg Med. 2007; 8: 176-189.
- 13. Abboud PA, Hake PW, Burroughs TJ, Odoms K, O'Connor M, Mangeshkar P, Wong HR, Zingarelli B. <u>Therapeutic effect of epigallocatechin-3-gallate in a mouse model of colitis</u>. *Eur J Pharmacol.* 2008; 579: 411-7.
- 14. Kaplan J, Cook JA, O'Connor M, Zingarelli B. Peroxisome proliferator-activated receptor gamma is required for the inhibitory effect of ciglitazone but not 15-deoxy-Delta 12,14-prostaglandin J2 on the NFkappaB pathway in human endothelial cells. *Shock.* 2007; 28: 722-726.
- 15. Page K, Lierl KM, Herman N, Wills-Karp M. Differences in susceptibility to German cockroach frass and its associated proteases in induced allergic inflammation in mice. Respir Res. 2007; 8: 91.
- 16. Page K, Lierl KM, Hughes VS, Zhou P, Ledford JR, Wills-Karp M. **TLR2-mediated activation of neutrophils in response to German cockroach frass.** *J Immunol.* 2008; 180: 6317-24.
- 17. Chase MA, Wheeler DS, Lierl KM, Hughes VS, Wong HR, Page K. **Hsp72 induces inflammation and regulates** cytokine production in airway epithelium through a TLR4- and NF-kappaB-dependent mechanism. *J Immunol.* 2007; 179: 6318-24.
- 18. Giuliano JS, Jr., Sekar P, Dent CL, Border WL, Hirsch R, Manning PB, Wheeler DS. Unilateral pulmonary edema

- and acute rheumatic fever. Eur J Pediatr. 2008; 167: 465-7.
- 19. Wheeler DS. Stress proteins and acute lung injury: dreams can come true... eventually. *Crit Care Med.* 2008; 36: 360-2.
- 20. Wheeler DS, Dauplaise DJ, Giuliano JS, Jr.. An infant with fever and stridor. Pediatr Emerg Care. 2008; 24: 46-9.
- 21. Wheeler DS, Dent CL, Manning PB, Nelson DP. Factors prolonging length of stay in the cardiac intensive care unit following the arterial switch operation. *Cardiol Young.* 2008; 18: 41-50.
- 22. Wheeler DS, Devarajan P, Ma Q, Harmon K, Monaco M, Cvijanovich N, Wong HR. Serum neutrophil gelatinase-associated lipocalin (NGAL) as a marker of acute kidney injury in critically ill children with septic shock. *Crit Care Med.* 2008; 36: 1297-303.
- 23. Wheeler DS, Wong HR. Genetic approach to pediatric septic shock. Pers Med. 2008; 5: 249-263.
- 24. Giuliano JS, Jr., Lahni PM, Harmon K, Wong HR, Doughty LA, Carcillo JA, Zingarelli B, Sukhatme VP, Parikh SM, Wheeler DS. **Admission angiopoietin levels in children with septic shock.** *Shock.* 2007; 28: 650-654.
- 25. Wong HR, Odoms K, Sakthivel B. <u>Divergence of canonical danger signals: the genome-level expression patterns of human mononuclear cells subjected to heat shock or lipopolysaccharide</u>. *BMC Immunol.* 2008; 9: 24.
- 26. Wong HR, Shanley TP, Sakthivel B, Cvijanovich N, Lin R, Allen GL, Thomas NJ, Doctor A, Kalyanaraman M, Tofil NM, Penfil S, Monaco M, Tagavilla MA, Odoms K, Dunsmore K, Barnes M, Aronow BJ. <u>Genome-level expression profiles in pediatric septic shock indicate a role for altered zinc homeostasis in poor outcome</u>. *Physiol Genomics*. 2007; 30: 146-55.
- 27. Fan H, Williams DL, Zingarelli B, Breuel KF, Teti G, Tempel GE, Spicher K, Boulay G, Birnbaumer L, Halushka PV, Cook JA. **Differential regulation of lipopolysaccharide and Gram-positive bacteria induced cytokine and chemokine production in macrophages by Galpha(i) proteins.** *Immunology.* 2007; 122: 116-23.
- 28. Irazuzta J, Pretzlaff RK, Zingarelli B. Caspases inhibition decreases neurological sequelae in meningitis. *Crit Care Med.* 2008; 36: 1603-6.
- 29. Kuboki S, Shin T, Huber N, Eismann T, Galloway E, Schuster R, Blanchard J, Zingarelli B, Lentsch AB. **Peroxisome** proliferator-activated receptor-gamma protects against hepatic ischemia/reperfusion injury in mice. *Hepatology*. 2008; 47: 215-24.
- 30. Zingarelli B, Fan H, Ashton S, Piraino G, Mangeshkar P, Cook JA. **Peroxisome proliferator activated receptor gamma is not necessary for the development of LPS-induced tolerance in macrophages.** *Immunology.* 2008; 124: 51-7.
- 31. Zingarelli B, Hake PW, Mangeshkar P, O'Connor M, Burroughs TJ, Piraino G, Denenberg A, Wong HR. **Diverse** cardioprotective signaling mechanisms of peroxisome proliferator-activated receptor-gamma ligands, 15-deoxy-Delta12,14-prostaglandin J2 and ciglitazone, in reperfusion injury: role of nuclear factor-kappaB, heat shock factor 1, and Akt. *Shock.* 2007; 28: 554-63.

Grants, Contracts, and Industry Agreements

Grant and Contract Awards

Annual Direct / Project Period Direct

Doughty, L

Viral Modulation of the Inflammatory Response

National Institutes of Health

K08 GM 071568 03/01/05 - 06/30/09 \$111,200 / \$488,968

Nowak, J

Host Response to Trauma Research Training Program

National Institutes of Health (University of Cincinnati)

T32 GM 008478 07/01/07 - 06/30/08 \$51,536 / \$51,536

Page, K

Role of Cockroach Proteases in Airway Inflammation

National Institutes of Health

R01 HL 075568 12/15/04 - 11/30/08 \$189,636 / \$800,000

Poynter, S

Exogenous Hsp70 Modulates Innate Immunity Through Increased Bacterial Clearance

National Institutes of Health (University of Utah)

K12 HD 047349 01/01/07 - 12/31/08 \$111,750 / \$178,625

		•	. ,
	Current	Year Direct Receipts	\$6,747
Discovery Laboratories, Inc.			\$ 6,747
Wheeler, D			
ndustry Contracts			
		Current Year Direct	\$1,081,863
R01 AG 027990	09/01/07 - 08/31/12		\$205,000 / \$1,025,000
Mechanisms of Age-Related Inflamma National Institutes of Health		nagic Shock	
R01 GM 027673	07/01/04 - 06/30/09		\$10,798 / \$63,569
Zingarelli, B Role of Eicosanoids in Shock National Institutes of Health (Medical Ur	•		\$40.700 / \$00.50
R01 GM 064619	09/01/07 - 08/31/10		\$221,597 / \$677,67 ₄
Genomic Analysis of Pediatric SIRS a National Institutes of Health	•		4004 507 44077 07
National Institutes of Health (Case Wes HHSN275200403367C	tern University) 04/01/05 - 03/31/08		\$68,355 / \$316,512
Wong, H. Pediatric Off-Patient Study Center for	r Lorazepam Sedation		
	04/01/00 00/01/11		Ψ111,0017 φ001,200
National Institutes of Health K08 GM 077432	04/01/06 - 03/31/11		\$111,991 / \$561,250