Sepsis

Wei Chao, MD, PhD, FAHA (wchao@som.umaryland.edu), Professor of Anesthesiology & Physiology. Dr. Chao is a Physician-Scientist and Co-Director of the Center for Shock, Trauma & Anesthesiology Research at the University of Maryland School of Medicine. His laboratory is interested in the molecular and cellular mechanisms of sepsis, traumatic injury, and ischemic myocardial injury, specifically the role of novel innate immune signaling in the pathogenesis of these critical illnesses. For these basic and translational studies, they use a combination of mouse genetics (transgenics and knockouts), physiology, biochemistry, and immunology. He has been PI on multiple grants from the NIH, DoD, and NSF. He has mentored both Ph.D. and M.D. scientists and his trainees have been successfully funded by various career development and independent research awards, such as NHLBI K08 Award and NIGMS ESI R35 Award.

Highlighted Publications:

1. Li Y, Feng Y, Chen H, Zou L, Si R, Wang E, Zhang M, Warren S, Sosnovik D, **Chao W.** Myocardial ischemia induces a rapid activation of innate immune signaling *via* cardiac heat-shock protein 60 and Toll-like receptor 4. *J Biol Chem.* 2011; 286:31308-19. PMID: 21775438

2. Chen C, Feng Y, Zou L, Chen HH, Cai JY, Xu JM, Sosnovik DE, **Chao W.** Role of extracellular RNA and TLR3-Trif signaling in myocardial ischemia-reperfusion injury. *J Am Heart Assoc.* 2014 Jan 3; 3(1): e000683. PMID: 24390148

3. Feng Y, Chen H, Cai J, Zou L, Yan D, Xu G, Li D, **Chao W.** Cardiac RNA induces inflammatory responses in cardiomyocytes and immune cells via Toll-like receptor 7 signaling. *J Biol Chem.* 2015; 290: 26688-98. PMID: 26363072.

4. Zou L, Feng Y, Xu G, Jian W, **Chao W.** Splenic RNA and microRNA mimics promote complement factor B production and alternative pathway activation via innate immune signaling. *J Immunol.* 2016; 196: 2788-98. PMID: 26889043.

5. Feng Y, Zou L, Yan D, Chen H, Xu G, Jian W, Cui P, **Chao W.** Extracellular microRNAs induce potent innate immune responses via TLR7/MyD88-dependent mechanisms. *J Immunol.* 2017; 199: 2106-17. PMID: 28768728.

6. Chen H., Yuan H., Cho H., Feng Y., Ngoy S., Kumar A., Liao R., **Chao W**., Josephson L., Sosnovik D.. Theranostic Nucleic Acid Binding Nanoprobe Exerts Anti-inflammatory and Cytoprotective Effects in Ischemic Injury. *Theranostics.* 2017. 7(4), 814-825. PMID: 28382156

7. Xu J, Feng Y, Jeyaram A, Jay SM, Zou L, **Chao W.** Circulating plasma extracellular vesicles from septic mice induce inflammation via microRNA- and TLR7-dependent mechanisms. *J Immunol.* 2018; 201: 3392-3400. PMID: 30355788

8. Jian W, Gu L, Williams B, Feng Y, **Chao W** and Zou L. Toll-like Receptor 7 Contributes to Inflammation, Organ Injury, and Mortality in Murine Sepsis. *Anesthesiology*. 2019; 131:105-118; PMID: 31045897

9. Williams B, Neder J, Cui P, Suen A, Tanaka K, Zou L and **Chao W.** Toll-like receptor 2 and 7 mediate coagulation activation and coagulopathy in murine sepsis. *J Thromb Haemost*. 2019; 17:1683-1693. PMID: 31211901

10. Jeyaram A, Lamichhane TN, Wang S, Zou L, Dahal E, Kronstadt SM, Levy D, Parajuli B, Knudsen DR, **Chao W,** Jay SM. Enhanced Loading of Functional miRNA Cargo via pH Gradient Modification of Extracellular Vesicles. *Mol Ther.* 2019 Dec 24 [Online ahead of print]. PMID: 31911034.

11. Chen F, Zou L, Williams B, and **Chao W**. Targeting Toll-Like receptors in sepsis - From bench to clinical trials. *Antioxid Redox Signal*. 2021; doi: 10.1089/ars.2021.0005. Online ahead of print. PMID: 33588628

Links:

Med School faculty page: http://www.medschool.umaryland.edu/profiles/Chao-Wei/

PubMed Publications:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1F3awzaP7DBkx/bibliography/47345926/public/?sort=date&direction=descending

Jeffrey Hasday (jhasday@som.umaryland.edu)**:** The Hasday lab has focused on how febrile-range hyperthermia and hypothermia modify biological processes relevant to disease pathogenesis with emphasis on acute lung injury/ARDS and fibrosis. Using approaches that span structural biology, gene and protein expression, cell culture, animal models and human trials, the Hasday laboratory has shown that hyperthermia worsens and hypothermia improves lung injury by modifying endothelial permeability, neutrophil recruitment, epithelial injury, and cytokine and heat shock protein expression. The p38 MAP kinase pathway appears to be a major contributor to the temperature-dependence of endothelial barrier function and expression of pro-inflammatory cytokines. The Hasday laboratory is currently has three areas of research: (1) the DoD-funded Cooling to Help Injured Lungs (CHILL) randomized clinical trial of mild hypothermia plus neuromuscular blockade vs. standard temperature management in patients with moderate to severe ARDS, a 14-center trial for which we serve as both the Data Coordinating Center and Clinical Coordinating Center; (2) expansion of our exciting data showing that the structure and function of p38alpha, the proinflammatory p38 family member, but not p38beta is temperature-dependent in the 33° to 39°C range; and (3) the computer-assisted design of a novel class of substrate- and function-selective inhibitors of p38alpha for treatment of acute lung injury; one of these novel drugs has just completed Phase 1 studies and will begin Phase 2 studies in the near future. Dr. Hasday also directs the University of Maryland Cytokine Core Laboratory (www.cytokines.com).

Highlighted Publications:

1. Shah NG, Tulapurkar ME, Ramarathnam A, Brophy A, Martinez R 3rd, Hom K, Hodges, T, Samadani R, Singh IS, MacKerell AD Jr, Shapiro P, Hasday JD. Novel Noncatalytic Substrate-Selective p38α-Specific MAPK Inhibitors with Endothelial-Stabilizing and Anti-Inflammatory Activity. J Immunol. 2017; 198(8):3296-3306. Pubmed PMID: 28298524.

2. Slack DF, Corwin DS, Shah NG, Shanholtz CB, Verceles AC, Netzer G, Jones KM, Brown CH, Terrin ML, Hasday JD. Pilot Feasibility Study of Therapeutic Hypothermia for Moderate to Severe Acute Respiratory Distress Syndrome. Crit Care Med. 2017 45:1152-59;PubMed PMID: 28406814.

3. Tulapurkar ME, Ramarathnam A, Hasday JD, Singh IS. Bacterial lipopolysaccharide augments febrile-range hyperthermia-induced heat shock protein 70 expression and extracellular release in human THP1 cells. PLoS One. 2015;10(2):e0118010. PubMed PMID: 25659128; PubMed Central PMCID: PMC4320107.

4. Gupta A, Cooper ZA, Tulapurkar ME, Potla R, Maity T, Hasday JD, Singh IS. Toll-like receptor agonists and febrile range hyperthermia synergize to induce heat shock protein 70 expression and extracellular release. J Biol Chem. 2013 Jan 25;288(4):2756-66. PubMed PMID: 23212905; PubMed Central PMCID: PMC3554941.

5. Tulapurkar ME, Almutairy EA, Shah NG, He JR, Puche AC, Shapiro P, Singh IS, Hasday JD. Febrile-range hyperthermia modifies endothelial and neutrophilic functions to promote extravasation. Am J Respir Cell Mol Biol. 2012 Jun;46(6):807-14. PubMed PMID: 22281986; PubMed Central PMCID: PMC3380289.

6. Shah NG, Tulapurkar ME, Damarla M, Singh IS, Goldblum SE, Shapiro P, Hasday JD. Febrile-range hyperthermia augments reversible TNF-α-induced hyperpermeability in human

microvascular lung endothelial cells. Int J Hyperthermia. 2012;28(7):627-35. PubMed PMID: 22834633.

7. Deredge, D., Wintrode, P., Tulapiurkar, M. E., Nagarsekar, A., Zhang, Y., Weber, D. J., Shapiro, P., and Hasday, J. D. (2019) A temperature-dependent conformational shift in p38 MAP kinase substrate binding region associated with changes in substrate phosphorylation profile. *J. Biol. Chem.* 2019;294:1264-37. PubMed PMID 31073086.

Links:

Med School faculty page: http://www.medschool.umaryland.edu/profiles/Hasday-Jeffrey/

PubMed publications:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40776367/?sort=date&direction=ascending

Alan Cross (across@som.umaryland.edu)**:** Dr. Cross' research focuses on the study of sepsis, including: (1) development of vaccines to prevent sepsis including development of multivalent vaccines for *P. aeruginosa, Klebsiella* and *E. coli* that progressed to phase 1 testing in human subjects; (2) study of glycobiology and sialic acid turnover as a druggable mechanism in innate host response and sepsis; (3) development of a pan-Gram-negative bacterial vaccine that targets the LPS core; (4) targeting the CD28/B7 axis to treat sepsis and ARDS; and (5) mechanisms of Gram-negative bacterial sepsis. He employs multiple animal models of respiratory, burn wound and disseminated infections.

Highlighted Publications:
1. Cross A, Opal SM, Palardy J, Shridhar S, Baliban S, Scott A, Chahin A, Ernst R. A pilot study of an anti-endotoxin immunoglobulin-enriched bovine colostrum to prevent experimental sepsis. Innate Immunity 2021: Apr 27(3):266-274 PMID: 33858

2. Feng C, Stamatos NM, Dragan A, Medvedev A, Whitford M, Zhang L, Song C, Rallabhandi, P, Nhu Q, Vogel SN, Geddes C, Cross AS. Sialyl residues modulate LPS-mediated signaling through the Toll-like receptor 4 complex. PLoS One 2012;7:e32359

3. Feng C, Zhang L, Almulki L, Faez S, Whitford M, Hafezi-Moghadam A, Cross AS. Endogenous PMN sialidase activity exposes activation epitope on CD11b/CD18 which enhances its binding interaction with ICAM-1. J. Leukoc. Biol. 2011;90:313-3214.

4. Ramachandran G, Tulapurkar ME2, Harris KM, Arad G, Shirvan A, Shemesh R, DeTolla LJ, Benazzi C, Opal SM, Kaempfer R, Cross AS. A peptide antagonist of CD28 signaling attenuates toxic shock and necrotizing soft tissue infection induced by Streptococcus pyogenes J. Infect Dis. 2013;207:1869-77. Epub 2013Mar14. PMID234937295.

5. Brammer J, Choi M, Baliban SM, Kambouris AR, Fiskum G, Chao W, Lopez K, Miller C, Al-Abed Y, Vogel SN, Simon R, Cross AS. A nonlethal murine flame burn model leads to a transient reduction in host defenses and enhanced susceptibility to lethal Pseudomonas aeruginosa. Infect Immun 2021: Jun 21:IAI0009121.doi: 10.1128/IAI0091-21. PMID: 34152806.

Links: Faculty webpage: http://www.medschool.umaryland.edu/profiles/Cross-Alan/

PubMed publications:
http://www.ncbi.nlm.nih.gov/sites/myncbi/alan.cross.1/bibliography/41139315/public/?sort=date&direction=ascending

Rosemary Kozar (RKozar@som.umaryland.edu)**:** Dr. Kozar's laboratory research focuses on the (1) molecular pathogenesis of hemorrhagic shock, (2) use of novel blood products to repair the endothelium and (3) the pathogenic role of multimeric von Willebrands Factor after hemorrhage in endothelial cell injury and coagulopathy and (5) role of extracellular vesicles in endothelial cell injury after injury.

Highlighted Publications:

1. Wu F, Wang JY, Chao W, Sims C, Kozar RA. miR-19b targets pulmonary endothelial syndecan-1 following hemorrhagic shock. Sci Rep. 2020 Sep 25;10(1):15811. doi: 10.1038/s41598-020-73021-3. PMID: 32978505; PMCID: PMC7519668.
2. Zeineddin A, Dong JF, Wu F, Terse P, Kozar RA. Role of Von Willebrand Factor after Injury: It May Do More Than We Think. Shock. 2021 Jun 1;55(6):717-722. doi: 10.1097/SHK.0000000000001690. PMID: 33156241.
3. Wu F, Kozar RA. Fibrinogen Protects Against Barrier Dysfunction Through Maintaining Cell Surface Syndecan-1 In Vitro. Shock. 2019 June 5(6):740-744. doi: 10.1097/SHK.0000000000001207. PMID: 29905671; PMCID: PMC6292777.
4. Wu F, Chipman A, Kozar RA. Fibrinogen activates PAK1/cofilin signaling pathway to protect endothelial barrier integrity. *Shock* 2021 May 1;55(5):660-665. PMID: 32433215.
5. Wu F, Chipman A, Pati S, Miyasawa B, Corash L, Kozar RA. Resuscitative Strategies to Modulate the Endotheliopathy of Trauma: From Cell to Patient. *Shock* 2020 May;53(5):575-584. doi: 10.1097/SHK.0000000000001378. PMID:31090680 PMCID: PMC6842415.

Links:

Med School faculty page: http://www.medschool.umaryland.edu/profiles/Kozar-Rosemary/

PubMed publications:
https://www.ncbi.nlm.nih.gov/myncbi/rosemary.kozar.2/bibliography/public/

Carl Shanholtz (Cshanhol@som.umaryland.edu): Dr. Shanholtz has had a longstanding interest in improving management of critically ill patients and has a long and successful record of clinical research in critical illness in general, and acute respiratory distress syndrome specifically. Together Dr. Roy Brower, Dr. Shanholtz conducted the phase II clinical trial of low tidal volume ventilation in ARDS on which the ARDSNet ALVEOLI study was based, and he has been site director for ARDSnet-I and II. Dr. Shanholtz also studies methods to reduce fluid administration to critically ill patients and is a co-investigator and Director of the Clinical Coordinating Center for Dr. Hasday's CHILL trial of therapeutic hypothermia in ARDS patients.

Highlighted Publications:

1. Netzer G, Dowdy DW, Harrington T, Chandolu S, Dinglas VD, Shah NG, Colantuoni E, Mendez-Tellez PA, Shanholtz C, Hasday JD, Needham DM. Fever is associated with delayed ventilator liberation in acute lung injury. Ann Am Thorac Soc. 2013 Dec;10(6):608-15. PubMed PMID: 24024608; PubMed Central PMCID: PMC3960965.

2. Shah NG, Cowan MJ, Pickering E, Sareh H, Afshar M, Fox D, Marron J, Davis J, Herold K, Shanholtz CB, Hasday JD. Nonpharmacologic approach to minimizing shivering during surface cooling: a proof of principle study. J Crit Care. 2012 Dec;27(6):746.e1-8. PubMed PMID: 22762936; PubMed Central PMCID: PMC3494806.

3. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med. 2000 May 4;342(18):1301-8. PubMed PMID: 10793162.

4. Brower RG, Shanholtz CB, Fessler HE, Shade DM, White P Jr, Wiener CM, Teeter JG, Dodd-o JM, Almog Y, Piantadosi S. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. Crit Care Med. 1999 Aug;27(8):1492-8. PubMed PMID: 10470755.

5. Slack DF, Corwin DS, Shah NG, Shanholtz CB, Verceles AC, Netzer G, Jones KM, Brown CH, Terrin ML, Hasday JD. Pilot Feasibility Study of Therapeutic Hypothermia for Moderate to Severe Acute Respiratory Distress Syndrome. Crit Care Med. 2017 45:1152-59;PubMed PMID: 28406814.

Links:

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PubMed publications:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/47839782/?sort=date&direction=ascending

Kari Ann Shirey (KShirey@som.umaryland.edu): Dr. Shirey's research focuses on the ability of pathogens, *e.g.*, *Francisella tularensis*, Respiratory Syncytial Virus (RSV), and influenza to modulate the host's innate immune response by altering macrophage differentiation (alternatively activated phenotype (M2)) and skewing toward a Th2-like phenotype (e.g., IL-4, IL-13, TSLP). A second aspect of Dr. Shirey's research studies host-directed approaches to identify novel therapeutics for pathogens that induce acute lung injury (ALI). By interfering with the host's innate immune response, it may be possible to control the production of potentially damaging cytokines and DAMPs and thereby mitigate the severity of infection. Dr. Shirey has established the critical role of TLR4 in influenza- induced pathology and lethality by first demonstrating that TLR4$^{-/-}$ mice are refractory to influenza-induced disease and, second, that multiple TLR4 antagonists, including Eritoran, block influenza-mediated acute lung injury even when administered late in infection. This work has been followed up with other small molecule inhibitors and neutralizing antibodies that have effectively blocked viral-induced acute lung injury and lethality in mice and cotton rats. Our finding that the cellular protein, HMGB1, is released into the circulation upon influenza and RSV infection, and correlates with disease severity in cotton rats, led to the finding that HMGB1, previously identified as a TLR4 agonist, mediates the lethality induced by influenza infection. More recently, Dr. Shirey identified a novel host-derived protein, gastrin releasing peptide (GRP), that when antagonized in influenza-infected mice, also blunts influenza-induced lethality, lung pathology, and cytokine gene expression. The data suggests a relationship between TLR4 signaling and signaling induced by GRP.

Highlighted Publications:

1. **Shirey K**, Pletneva LM, Puche AC, *Keegan AD*, Prince GA, Blanco JC, and Vogel SN. (2010). Control of RSV-induced lung injury by alternatively activated macrophages is IL-4Ra-. TLR4-, and IFN-b- dependent. *Mucosal Immunol*. 3:291-300. PMC2875872

2. **Shirey KA**, Lai W, Scott AJ et al. (2013) The TLR4 antagonist, Eritoran, protects mice from lethal influenza infection. *Nature* 497:498-502. PMC3725830 See accompanying podcast interview.
3. **Shirey KA**, Lai W, Pletneva LM et al. (2014) Agents that increase alternatively activated macrophage differentiation blunt Respiratory Syncytial Virus-mediated lung pathology. *J. Leukoc. Biol.* 96: 951-955. PMC4226793 See accompanying editorial.
4. **Shirey KA**, Lai W, Patel MC et al. (2016). Novel strategies for targeting innate immune responses to influenza. *Mucosal Immunol*. 9:1173-82. PMC5125448
5. **Shirey KA**, Perkins DJ, Lai W, Zhang W, Fernando LR, Gusovsky F, Blanco JCG, Vogel SN. (2019) Influenza "trains" the host for enhanced susceptibility to secondary bacterial infection. mBio May 7;10(3):e00810-19. Doi:10:1128/mBio.00810-19. PMC6509193.

6. **Shirey KA**, Sunday ME, Lai W, Patel MC, Blanco JCG, Cuttitta F, Vogel SN. (2019). Novel role of gastrin releasing peptide-mediated signaling in the host response to influenza infection. *Mucosal Immunol.* 12:223-231. PMC6301097

7. **Shirey KA**, Blanco JCG, Vogel SN. (2021) Targeting TLR4 signaling to blunt viral-mediated acute lung injury. Front Immunol. Jul 2;12:705080. Doi:10.3389/fimmu.2021.705080.

Links:

Med School Faculty page: https://www.medschool.umaryland.edu/profiles/Shirey-Kari-Ann/

Pubmed publications: https://www.ncbi.nlm.nih.gov/myncbi/1xQKiut_y7t5X/bibliography/public/

Stefanie Vogel (svogel@som.umaryland.edu)**:** Dr. Vogel's focuses on the innate immune response to infection, the mechanisms by which inflammatory responses are regulated, macrophage differentiation and disease outcome, and targeting TLR signaling pathways to blunt pathogen-mediated acute lung injury. Dr. Vogel's most recent work has identified novel strategies for treating influenza therapeutically by blocking Toll-like receptor 4 signaling, the role of metabolism in the differentiation of macrophages, the cross-talk between innate immune signaling pathways, and other related topics, such as Innate immune responses to respiratory infections.

Highlighted Publications:

1. K. A. Shirey, W. Lai, A. J. Scott, M. Lipsky, P. Mistry, L. M. Pletneva, C. L. Karp, J. McAlees, T. L. Gioannini, J. Weiss, W. H. Chen, R, K. Ernst, D. P. Rossignol, F. Gusovsky, J. C. Blanco, and S. N. Vogel. The TLR4 antagonist, Eritoran, protects mice from lethal influenza infection. *Nature* 497:498-502 (2013) PMC3725830

2. K. A. Shirey, W. Lai, L. M. Pletneva, F. D. Finkelman, D. J. Feola, J. C. G. Blanco, and S. N. Vogel. Agents that increase alternatively activated macrophage differentiation blunt Respiratory Syncytial Virus-mediated lung pathology. *J. Leukoc. Biol.* 96: 951-955. PMC4226793. (2014). See accompanying editorial.

3. K. A. Shirey, W. Lai, M. C. Patel, L. M. Pletneva, G. Pang, E. Kurt-Jones, M. Lipsky, T. Roger, T. Calandra, K. J. Tracey, Y. Al-Abed, A. G. Bowie, A. Fasano, C. A. Dinarello, F. Gusovsky, J. C. G. Blanco , S. N. Vogel. Novel strategies for targeting innate immune responses to influenza. *Mucosal Immunol*. 9: 1173-1182. (2016). PMC5125448

4. K. Richard, D. J. Perkins, K. E. M. Harberts, Y. Song, A. Gopalakrishnan, K.A. Shirey, W. Asi, A. Vlk, A. Mahukar, S. Nallar, L. D. Hawkins, R. K. Ernst, S. N. Vogel. Dissociation of TRIF bias and adjuvanticity. *Vaccine* (2020) 38: 4298-4308. PMC7302928

5. K. Richard, K.H. Piepenbrink, K. A. Shirey, A. Gopalakrishnan, S. Nallar, D. J. Prantner, D. J. Perkins, W. Lai, A. Vlk, V. Y. Toshchakov, C. Feng, R. Fanaroff, A. E. Medvedev, J. C. G. Blanco, and S. N. Vogel. Human TLR4 D299G/T399I SNPs: A novel mouse model reveals mechanisms of altered pathogen sensitivity *J Exp Med* (2021) 218 (2): e20200675 (online ahead of print) PMC7685774

6. K.A. Shirey, J. C. G. Blanco, S. N. Vogel. Targeting TLR4 signaling to blunt viral-mediated acute lung injury. *Front Immunol* 02 July 2021. Doi:10.3389/fimmu.2021.705080 (2021). PMC – in process.

Links:

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