ARDS

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

Anna Birukova (abirukova@som.umaryland.edu): Dr. Birukova's research addresses mechanisms of cytoskeletal regulation of lung inflammation and resolution of acute lung injury with focus on microtubule (MT)-associated signaling and endothelial barrier function. Her prior studies showed a link between MT disassembly, activation of small GTPase RhoA, and leak in human lung endothelial cells (EC). She found that Rho activation is triggered by the MT-bound Rho-specific guanine nucleotide exchange factor, GEF-H1. Cyclic-AMP suppresses Rho signaling and EC permeability by stabilizing MT. This MT-dependent pathway is activated by pathologic (high amplitude) cyclic stretch as well as vasoactive and pro-inflammatory agonists such as TGFβ and TNFα. Importantly for recovery from acute lung injury/ARDS, Dr. Birukova has discovered that stimulation of MT growth promotes restoration of peripheral cytoskeleton, cell junctions, and EC barrier integrity by facilitating activation of Rac GTPase. Dr. Birukova made the interesting and clinically relevant observation that unlike pathologic stress, physiologic cyclic stretch accelerates restoration of endothelial barrier function through Rap1 GTPase- and cingulin-dependent downregulation of RhoA signaling.

Highlighted Publications:

1. Kratzer E, Tian Y, Sarich N, Wu T, Meliton A, Leff A, Birukova AA. ROS-mediated microtubule destabilization triggers GEF-H1-dependent endothelial permeability and inflammation in septic lung injury. *Am J Resp Cell Mol Biol,* 2012; 47(5): 688-697.

2. Tian Y, Tian X, Gawlak G, O'Donnel JO, Sacks DB, Birukova AA. IQGAP1 regulates endothelial barrier function via EB1 - cortactin crosstalk. *Mol Cell Biol.* 2014; 34(18): 3546-3558.

3. Tian Y, Gawlak G, Tian X, Shah A, Sarch N, Citi S, Birukova AA. Role of cingulin in agonist-induced vascular endothelial permeability. *J Biol Chem.* 2016; 291(45): 23681-23692.

4. Tian X, Ohmura T, Shah AS, Son S, Tian Y, Birukova AA. Role of End Binding Protein-1 in endothelial permeability response to barrier-disruptive and barrier-enhancing agonists. *Cell Signal.* 2017; 29: 1-11.

5. Ke Y, Karki P, Zhang C, Li Y, Nguyen T, Birukov KG, Birukova AA. Mechanosensitive Rap1 activation promotes barrier function of lung vascular endothelium under cyclic stretch. *Mol Biol Cell*. 2019;30:959-974

6. Karki P, Meliton A, Sitikov A, Tian Y, Ohmura T, Birukova AA. Microtubule destabilization caused by particulate matter contributes to lung endothelial barrier dysfunction and inflammation. *Cell Signal*. 2019;53:246-255

7. Karki P, Ke Y, Tian Y, Ohmura T, Sitikov A, Sarich N, Montgomery CP, Birukova AA. Staphylococcus aureus-induced endothelial permeability and inflammation are mediated by microtubule destabilization. *J Biol Chem*. 2019;294:3369-3384

Links:

Med School faculty page: http://www.medschool.umaryland.edu/profiles/Birukova-Anna/

PubMed publications: https://www.ncbi.nlm.nih.gov/pubmed/?term=birukova+anna

Konstantin Birukov (kbirukov@som.umaryland.edu)**:** Dr. Birukov's research is aimed at better understanding of molecular events driving onset and resolution of acute lung injury and development of new therapies to mitigate pathologic signaling leading to ARDS. The studies cover several areas, including: a) role of circulating danger associated molecular patterns (DAMPs) as biomarkers and pathogenic factors augmenting ARDS; b) synergy between mechanical stretch, tissue stiffness and bacterial pathogens in propagation of lung injury and inflammation; c) control of endothelial function by mechanical forces; d) role of oxidized phospholipids in lung pathobiology and development of new phospholipid-based therapeutics. His laboratory uses advanced biophysical and imaging methods, endothelial cell culture models of mechanical stress, and animal models of lung injury to understand the autoregulatory cascades providing recovery and resolution of acute lung injury. He developed a new area of research addressing novel, barrier-protective and anti-inflammatory properties of oxidized phospholipids and proposed a new group of synthetic phospholipase resistant lipid mediators for future treatment of lung injury, inflammation and vascular barrier dysfunction.

Highlighted Publications:

1. Everitt ML, Boegner DJ, Birukov KG, White IM. Sample-to-answer diagnostic system for the detection of circulating histones in whole blood. *ACS Sens*. 2021

2. Wyman AE, Nguyen TTT, Karki P, Tulapurkar ME, Zhang CO, Kim J, Feng TG, Dabo AJ, Todd NW, Luzina IG, Geraghty P, Foronjy RF, Hasday JD, Birukova AA, Atamas SP, Birukov KG. Sirt7 deficiency suppresses inflammation, induces EndoMT, and increases vascular permeability in primary pulmonary endothelial cells. *Sci Rep*. 2020;10:12497

3. Kim J, Nguyen TTT, Li Y, Zhang CO, Cha B, Ke Y, Mazzeffi MA, Tanaka KA, Birukova AA, Birukov KG. Contrasting effects of stored allogeneic red blood cells and their supernatants on permeability and inflammatory responses in human pulmonary endothelial cells. *Am J Physiol Lung Cell Mol Physiol*. 2020;318:L533-L548

4. Karki P, Birukov KG, Birukova AA. Extracellular histones in lung dysfunction: A new biomarker and therapeutic target? *Pulm Circ*. 2020;10:2045894020965357

5. Karki P, Birukov KG. Oxidized phospholipids in healthy and diseased lung endothelium. *Cells*. 2020;9

6. Ke Y, Karki P, Kim J, Son S, Berdyshev E, Bochkov VN, Birukova AA, Birukov KG. Elevated truncated oxidized phospholipids as a factor exacerbating ALI in the aging lungs. *FASEB J*. 2019;33:3887-3900

7. Fang Y, Wu D, Birukov KG. Mechanosensing and mechanoregulation of endothelial cell functions. *Compr Physiol*. 2019;9:873-904

8. Karki P, Meliton A, Shah A, Tian Y, Ohmura T, Sarich N, Birukova AA, Birukov KG. Role of truncated oxidized phospholipids in acute endothelial barrier dysfunction caused by particulate matter. *PLoS One*. 2018;13:e0206251

Links:
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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:

Med School faculty page: http://www.medschool.umaryland.edu/profiles/Shanholtz-Carl/

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

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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