Drug Development

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.

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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

Paul Shapiro (pshapiro@rx.umaryland.edu): The primary objective of the Shapiro laboratory is to identify novel small molecular weight compounds that can selectively disrupt the interactions between protein kinases and substrate proteins to afford a more specific manipulation of signaling networks involved in disease. The experimental approach integrates computational chemistry with structural and functional cell biology. The laboratory has focused on identifying compounds that interact with unique docking sites on the extracellular signal regulated kinases (ERKs) and p38 and disrupt phosphorylation of select protein substrates. The ERK inhibitors are being tested in models of cancer and the airway smooth muscle hypertrophy that occurs in asthma. The p38 inhibitors developed in collaboration with Dr. Hasday, are being developed as anti-inflammatory agents and tested in models of acute lung injury.

Highlighted Publications:

1. Chad N. Hancock, Alba Macias, Eun Kyoung Lee, Su Yeon Yu, Alexander D. MacKerell, Jr., and Paul Shapiro (2005) Identification of novel extracellular signal-regulated kinase (ERK) docking domain inhibitors. *Journal of Medicinal Chemistry*, 48:4586-4595. PMID: 15999996

2. Fengming Chen, Chad N. Hancock, Alba T. Macias, Joseph Joh, Kimberly Still, Shijun Zhong, Alexander D. MacKerell, and Paul Shapiro (2006) Characterization of ATP-independent ERK inhibitors identified through in silico analysis of the active ERK2 structure. *Bioorganic Medicinal Chemistry Letters,* 16:6281-6287. PMID: 17000106

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4. Kira G. Hartman, Michele I. Vitolo, Adam D. Pierce, Jennifer M. Fox, Paul Shapiro, Stuart S. Martin, Paul T. Wilder and David J. Weber. (2014) Complex formation between S100B and the p90 ribosomal S6 kinase (RSK) in malignant melanoma is Ca^{2+}-dependent and inhibits ERK-mediated phosphorylation of RSK. *J. Biol. Chem*. 289(18):12886-95. PMID:24627490

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Links:

Med School faculty page: http://faculty.rx.umaryland.edu/pshapiro/

PubMed publications: http://www.ncbi.nlm.nih.gov/pubmed/?term=Shapiro+P+Maryland

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

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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

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Links:
Med School faculty page: http://www.medschool.umaryland.edu/profiles/Birukov-Konstantin/

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

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

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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

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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

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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

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

Christine Lau: Dr. Lau is Professor and Chair of the Department of Surgery at the University of Maryland, a thoracic surgeon specializing in lung transplantation, and a surgeon-scientist. Her research focuses on the pathogenesis and prevention of lung transplant rejection. Specifically, she has studied (1) biomarkers of bronchiolitis obliterans focusing on the CXCR4/CXCL12 axis,

NKT cells, and loss of epithelial cells; and (2) the therapeutic potential of adenosine analogs in mitigating lung transplant injury utilizing a porcine ex vivo lung perfusion and preclinical models.

Highlighted Publications:

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4. Lau CL, Zhao Y, Kron IL, Stoler MH, Laubach VE, Ailawadi G, Linden J. (2009) The role of adenosineA2A receptor signaling in bronchiolitis obliterans. Ann Thorac Surg. 88(4):1071-8.

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9. Zhao Y, Gillen JR, Harris DA, Kron IL, Murphy MP, Lau CL. Treatment with placenta-derived mesenchymal stem cells mitigates development of bronchiolitis obliterans in a murine model. J ThoracCardiovasc Surg. 2014 May;147(5):1668-1677

10. Stone ML; Sharma AK; Mas VR; Gehrau RC; Mulloy DP; Zhao Y; Lau CL; Kron IL; Huerter ME; Laubach VE. Ex Vivo Perfusion With Adenosine A2A Receptor Agonist Enhances Rehabilitation ofMurine Donor Lungs After Circulatory Death. Transplantation. 99(12):2494-503, 2015.

Links:
Med School faculty page: https://www.medschool.umaryland.edu/profiles/Lau-Christine/