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. Dr. Hasday is expanding on his open-label trial of therapeutic hypothermia in ARDS by currently conducting a randomized clinical trial of hypothermia vs. standard temperature management in patients with ARDS. 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 following up on 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. Finally, the Hasday laboratory in collaboration with Dr. Paul Shapiro in the School of Pharmacy is designing novel p38alpha inhibitors that target the substrate binding domain rather than the catalytic domain of p38alpha. These novel compounds modify rather than inactivate its downstream signaling, are superior to conventional catalytic p38 inhibitors in preclinical testing, and are being developed into potential new drugs to treat ARDS and other inflammatory diseases. 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.

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. Amy E. Defnet, Jeffrey D. Hasday, **Paul Shapiro** (2020) Kinase inhibitors in the treatment of obstructive pulmonary diseases, *Current Opinion in Pharmacology,* Vol. 511:11-18.

2. Amy E. Defnet, Weiliang Huang, Steven Polischak, Santosh Kumar Yadav, Maureen A. Kane, **Paul Shapiro***, and Deepak A Deshpande*. Effects of ATP-Competitive and Function-Selective ERK Inhibitors on Airway Smooth Muscle Cell Proliferation. (2019) *FASEB J*. Jul 2:fj201900680R, PMID:31266368
*Co-corresponding authors

3. Daniel Deredge, Patrick L. Wintrode, Mohan E. Tulapurkar, Ashish Nagarsekar, Yingua Zhang, David J. Weber, **Paul Shapiro**, and Jeffrey D. Hasday (2019) Temperature-dependent Conformational Shift in p38a MAP Kinase Substrate Binding Region and Associated Change in Substrate Phosphorylation Profile. *J Biol Chem.* 294(34), 12624-12637. PMID:31213525.

4. 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. (2017) Novel Noncatalytic Substrate-Selective p38α-Specific MAPK Inhibitors with Endothelial-Stabilizing and Anti-Inflammatory Activity. *J Immunol.*, 198(8):3296-3306. PMID: 28298524

5. Samadani R, Zhang J, Brophy A, Oashi T, Priyakumar UD, Raman EP, St John FJ, Jung KY, Fletcher S, Pozharski E, MacKerell AD, **Shapiro PS** (2015). Small Molecule Inhibitors of ERK-mediated Immediate Early Gene Expression and Proliferation of Melanoma Cells Expressing Mutated BRaf. *Biochem J.* Volume 467 (part 3), p425-438. PMCID: PMC4643458

Links:
Med School faculty page: http://faculty.rx.umaryland.edu/pshapiro/
PubMed publications: http://www.ncbi.nlm.nih.gov/pubmed/?term=Shapiro+P+Maryland