Lung Infections

Nicholas Carbonetti (ncarbonetti@som.umaryland.edu)**:** Dr. Carbonetti studies the pathogenesis of infection and disease caused by *Bordetella pertussis*, the agent of the respiratory disease pertussis (whooping cough). His lab uses a combination of animal models and in vitro approaches to investigate this host-pathogen interaction, with an emphasis on the host response. Current projects include: (i) investigation of the role of type I and III interferons in lung inflammatory pathology in adult mice and in protection against lethal disease in infant mice; (ii) determining the mechanism of action and therapeutic potential of sphingosine-1-phosphate receptor-targeted drugs in reducing pertussis-induced lung pathogenesis; (iii) investigation of age-dependent protective host responses, including the role of NK cells and interferon gamma in susceptibility of infant mice to lethal disease; and (iv) investigation of pertussis pathogenesis, including pulmonary hypertension and leukocytosis, in neonatal mouse models.

Highlighted Publications:

1. Scanlon, KM, Chen, L, Carbonetti, NH (2021) Pertussis toxin-dependent pulmonary hypertension in an infant mouse model of *Bordetella pertussis* infection. *Journal of Infectious Diseases*, Jun 19:jiab325. Online ahead of print
2. Ardanuy, JG, Scanlon, KM, Skerry, C, Fuchs, SY, Carbonetti, NH (2020) Age-dependent effects of type I and type III interferons in the pathogenesis of *Bordetella pertussis* infection and disease. *Journal of Immunology*. 204(8):2192-2202
3. Skerry, C, Goldman, WE, Carbonetti, NH (2019) Peptidoglycan recognition protein 4 suppresses early inflammatory responses to *Bordetella pertussis* and is required for sphingosine-1-phosphate receptor agonist-mediated attenuation of disease. *Infection and Immunity* 87(2):e00601-18
4. Scanlon, KM, Skerry, C, Carbonetti, NH (2019) Association of pertussis toxin with severe pertussis disease. *Toxins* 11, e373
5. Scanlon, KM, Snyder, YG, Skerry, C, Carbonetti, NH (2017) Fatal pertussis in the neonatal mouse model is associated with pertussis toxin-mediated pathology beyond the airways. *Infection and Immunity* 85(11): e00355-17
6. Skerry, C, Scanlon, KM, Ardanuy, JG, Roberts, D, Zhang, L, Rosen, H, Carbonetti, NH (2017) Reduction of pertussis inflammatory pathology by therapeutic treatment with sphingosine-1-phosphate receptor ligands by a pertussis toxin-insensitive mechanism. *Journal of Infectious Diseases* 215:278-286

Links:

Med School faculty page: http://www.medschool.umaryland.edu/profiles/Carbonetti-Nicholas/

PubMed Publications:
https://www.ncbi.nlm.nih.gov/sites/myncbi/nicholas.carbonetti.1/bibliography/41153362/public/?sort=date&direction=ascending

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

Wilbur Chen (WCHEN@som.umaryland.edu)**:** Dr. Chen is the Chief of the Adult Clinical Studies section, University of Maryland Center for Vaccine Development (CVD), which focuses on the development and clinical testing of vaccines for the infectious diseases. Dr. Chen's research focuses on development and testing of vaccines including for the pulmonary pathogens, influenza and tularemia, and for enteric and other infections. The CVD is a global program that offers opportunities to test vaccines in third world settings.

Highlighted Publications:

1. Chen WH, Toapanta F, Shirey KA, Zhang L, Giannelou A, Page C, Frieman M, Vogel S, and Cross AS. Potential Role for Alternatively Activated Macrophages in the Secondary Bacterial infection During Recovery from Influenza. *Immunology Letters* 2012; 141:227-34.

2. Shirey KA, Lai W, Scott A, Lipsky M, Mistry P, Pletneva LM, Karp CL, McAlees J, Gioannini JL, Weiss J, Chen WH, Ernst R, Rossignol DP, Gusovsky F, Blanco JC, Vogel SN. The TLR4 Antagonist, Eritoran, Protects Mice from Lethal Influenza Infection. *Nature* 2013; 497:498-502.

3. Chen WH, Jackson LA, Edwards KM, Keitel WA, Hill H, Noah DL, Creech CB, Patel SM, Mangal B, Kotloff KL. Safety, Reactogenicity, and Immunogenicity of Inactivated Monovalent Influenza A/H5N1 Virus Vaccine Administered With or Without AS03 Adjuvant. *Open Forum Infect Dis* 2014; 1(3):ofu091.

4. Chen WH, Jackson LA, Edwards KM, Keitel WA, Hill H, Noah DL, Creech CB, Patel SM, Mangal B, Kotloff KL. Persistence of Antibody to Influenza A/H5N1 Vaccine Virus: Impact of AS03 Adjuvant. *Clin Vacc Immunol* 2015; 23:73-77.

5. Chen WH, Pasetti MF, Adhikari RP, Baughman H, Douglas R, El-Khorazaty J, Greenberg N, Holtsberg FW, Liao GC, Reymann MK, Wang X, Warfield KL, Aman MJ. The safety and immunogenicity of a parenterally administered structure-based rationally modified recombinant Staphylococcal enterotoxin B protein vaccine, STEBVax. *Clin Vacc Immunol* 2016; 23: 918-25.

Links:

Med School faculty page: http://www.medschool.umaryland.edu/profiles/Chen-Wilbur/

PubMed publications:
http://www.ncbi.nlm.nih.gov/sites/myncbi/wilbur.chen.1/bibliography/40322237/public/?sort=date&direction=ascending

Justin Ortiz (jortiz@som.umaryland.edu)**:** Dr. Ortiz is a pulmonary and critical care medicine physician working in the UMSOM Center for Vaccine Development and Global Health. He has expertise in the clinical epidemiology and prevention of pneumonia. From 2014-2017, he was a Medical Officer at the World Health Organization Immunization Department where he led influenza vaccine activities. Dr. Ortiz' research interests focus on respiratory virus infection and immune response, impact modelling, and clinical trials. He is a Co-PI for the Collaborative Influenza Vaccine Innovation Centers (CIVICs) Clinical Core, leading human challenge studies of influenza virus and phase 1 clinical vaccine trials. He leads several modelling studies on the impact of RSV infection and prevention in young children in the US and in low-resource settings. Finally, working with colleagues from UMB and UMCP, he is designing inpatient influenza studies to better understand routes of influenza transmission. He and his team have many opportunities for trainees interested in clinical research.

Highlighted Publications:

1. Riddell CA, Bhat N, Bont LJ, Dupont WD, Feikin DR, Fell DB, Gebretsadik T, Hartert TV, Hutcheon JA, Karron RA, Nair H, Reiner RC, Shi T, Sly PD, Stein RT, Wu P, Zar HJ, **Ortiz JR** for the WHO Technical Working Group on Respiratory Syncytial Virus Vaccination During Pregnancy to Prevent Recurrent Childhood Wheezing. Informing randomized clinical trials of respiratory syncytial virus vaccination during pregnancy to prevent recurrent childhood wheezing: a sample size analysis. Vaccine. 2018 Dec 18;36(52):8100-8109. doi: 10.1016/j.vaccine.2018.10.041. Epub 2018 Nov 22. PubMed PMID: 30473186.
2. Somayaji R, Neradilek M, Szpiro AA, Lofy K, Goss CH, Jackson ML, Duchin JS, Neuzil KM, **Ortiz JR**. Impact of Air Pollution and Other Environmental Exposures on Estimates of Severe Influenza Illness. Emerg Infect Dis. 2020 May;26(5). doi: 10.3201/eid2605.190599. PubMed PMID: 32310747.
3. Laufer RS, Driscoll AJ, Baral R, Buchwald AG, Campbell JD, Coulibaly F, Diallo F, Doumbia M, Feikin DR, Galvani AP, Haidara F, Kotloff KL, Keita AM, Neuzil KN, Orenstein E, Pecenka C, Sow S, Tapia MD, **Ortiz JR**, Fitzpatrick MC. Cost-effectiveness of infant respiratory syncytial virus preventive interventions in Mali: A modeling study to inform policy and investment decisions. Vaccine. 2021 Jul 26:S0264-410X(21)00848-3. doi: 10.1016/j.vaccine.2021.06.086. Epub ahead of print. PMID: 34325934.
4. Williams SR, Driscoll AJ, LeBuhn HM, Chen WH, Neuzil KM, **Ortiz JR**. National Routine Adult Immunization Programs among World Health Organization Member States: An Assessment of Health Systems to Deploy Future SARS-CoV-2 Vaccines. Euro Surveill. 2021 Apr;26(17). doi: 10.2807/1560-7917.ES.2021.26.17.2001195. PMID: 33928899.
5. **Ortiz JR**, Yu SL, Driscoll AJ, Williams SR, Robertson J, Hsu JS, Chen WH, Biellik RJ, Sow S, Kochhar S, Neuzil KM. The operational feasibility of vaccination programs targeting influenza

risk groups in the WHO African and South-East Asian Regions. Clin Infect Dis. 2021 May 5:ciab393. doi: 10.1093/cid/ciab393. Epub ahead of print. PMID: 33949661.
6. **Ortiz JR**, Robertson J, Hsu JS, Yu SL, Driscoll AJ, Williams SR, Chen WH, Fitzpatrick MC, Sow S, Biellik RJ, Neuzil KM. The potential effects of deploying SARS-Cov-2 vaccines on cold storage capacity and immunization workload in countries of the WHO African Region. Vaccine. 2021 Apr 8;39(15):2165-2176. doi: 10.1016/j.vaccine.2021.02.037. Epub 2021 Feb 19. PMID: 33744049; PMCID: PMC7894202.
7. Brunwasser SM, Donovan BM, Driscoll AJ, Fell DB, Savitz DA, Feikin DR, Skidmore B, Bhat N, Bont LJ, Dupont WD, Wu P, Gebretsadik T, Holt PG, Zar HJ, **Ortiz JR**, Hartert TV#. Assessing the strength of evidence for a causal effect of respiratory syncytial virus lower respiratory tract infections on subsequent wheezing illness: a systematic review and meta-analysis. Lancet Respir Med. 2020 Aug;8(8):795-806. doi: 10.1016/S2213-2600(20)30109-0. Erratum in: Lancet Respir Med. 2021 Jan;9(1):e10. PMID: 32763206; PMCID: PMC7464591. #Co-senior authorship.

Links:

Med School faculty page: http://www.medschool.umaryland.edu/profiles/Ortiz-Justin/

PubMed publications:
https://www.ncbi.nlm.nih.gov/sites/myncbi/justin.ortiz.1/bibliography/40490877/public/?sort=date&direction=ascending