

## Viral Lung Disease/Flu

**Wilbur Chen** ([WCHEN@som.umaryland.edu](mailto: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, Holsberg 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>

**Matt Frieman** ([MFrieman@som.umaryland.edu](mailto:MFrieman@som.umaryland.edu)): Dr. Frieman's research focused on how respiratory viruses cause disease with a specific interest in Coronaviruses. The Frieman laboratory uses both *in vitro* and *in vivo* models of replication and pathogenesis to study the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1), SARS-CoV-2 and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). The lab is currently focused on a wide variety of therapeutics for SARS-CoV-2 in vitro and in mouse models of pathogenesis.

### Highlighted Publications:

1. Pascal KE, Coleman CM, Mujica AO, Kamat V, Badithe A, Fairhurst J, Hunt C, Strein J, Berrebi A, Sisk JM, Matthews KL, Babb R, Chen G, Lai KM, Huang TT, Olson W, Yancopoulos GD, Stahl N, Frieman MB, Kyratsous CA. Pre- and postexposure efficacy of fully human antibodies against Spike protein in a novel humanized mouse model of MERS-CoV infection. *Proc Natl Acad Sci U S A*. 2015 Jul 14;112(28):8738-43. PubMed PMID: 26124093; PubMed Central PMCID: PMC4507189.

2. Dyal J, Coleman CM, Hart BJ, Venkataraman T, Holbrook MR, Kindrachuk J, Johnson RF, Olinger GG Jr, Jahrling PB, Laidlaw M, Johansen LM, Lear-Rooney CM, Glass PJ, Hensley LE, Frieman MB. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. *Antimicrob Agents Chemother.* 2014 Aug;58(8):4885-93. PubMed PMID: 24841273; PubMed Central PMCID: PMC4136000.
3. Page C, Goicochea L, Matthews K, Zhang Y, Klover P, Holtzman MJ, Hennighausen L, Frieman M. Induction of alternatively activated macrophages enhances pathogenesis during severe acute respiratory syndrome coronavirus infection. *J Virol.* 2012 Dec;86(24):13334-49. PubMed PMID: 23015710; PubMed Central PMCID: PMC3503056.
4. Coleman CM, Sisk JM, Halasz G, et al. CD8+ T Cells and Macrophages Regulate Pathogenesis in a Mouse Model of Middle East Respiratory Syndrome. *Journal of Virology.* 2017;91(1):e01825-16. doi:10.1128/JVI.01825-16.

Links:

Med School faculty page: <http://www.medschool.umaryland.edu/profiles/Frieman-Matthew/>

PubMed publications:

<https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41149728/?sort=date&direction=ascending>

**Don Milton** ([dmilton@umd.edu](mailto:dmilton@umd.edu)): Dr. Milton's work focuses on the interrelated areas of infectious bioaerosols, exhaled breath analysis, and development and application of innovative methods for respiratory epidemiology. His work has been especially relevant to the current COVID-19 pandemic. During the height of the pandemic, Milton led NIH-, CDC-, and Bill and Melinda Gates Foundation-funded research to quantify infectious exhaled aerosols produced by COVID-19 cases using his patented exhaled breath samplers. This work directly examined the impact of face masks on SARS-CoV-2 shedding. Fellows working in his lab will have the opportunity to participate in a variety of federally funded research projects. Currently the lab is working on development and testing of innovative non-invasive measurement of deep lung biomarkers with a transdisciplinary team of engineers, molecular biologists, and photonics experts. Dr. Milton is also performing molecular epidemiologic studies of the importance of the airborne mode in transmission of influenza and other respiratory viruses using whole genome sequencing of viruses from exhaled breath aerosols and NP swabs to identify the source of transmitted viruses.

Highlighted Publications:

1. Yan J, Grantham M, Pantelic J, Bueno de Mesquita PJ, Albert B, Liu F, Ehrman S, Milton DK. Infectious virus in exhaled breath of symptomatic seasonal influenza cases from a college community. *Proc Natl Acad Sci U S A.* 2018 Jan 30;115(5):1081-1086. PubMed PMID: 29348203; PMCID: PMC5798362.
2. Milton DK, Fabian MP, Cowling BJ, Grantham ML, McDevitt JJ. Influenza virus aerosols in human exhaled breath: particle size, culturability, and effect of surgical masks. *PLoS Pathog.* 2013 Mar;9(3):e1003205. PubMed PMID: 23505369; PMCID: PMC3591312.
3. Fabian P, Brain J, Houseman EA, Gern J, Milton DK. Origin of exhaled breath particles from healthy and human rhinovirus-infected subjects. *J Aerosol Med Pulm Drug Deliv.* 2011 Jun;24(3):137-47. PubMed PMID: 21361786; PMCID: PMC3123971.
4. Shorter JH, Nelson DD, McManus JB, Zahniser MS, Sama SR, Milton DK. Clinical study of multiple breath biomarkers of asthma and COPD (NO, CO(2), CO and N(2)O) by infrared laser spectroscopy. *J Breath Res.* 2011 Sep;5(3):037108. PMCID: PMC3169766
5. Roy CJ, Milton DK. Airborne transmission of communicable infection--the elusive pathway. *N Engl J Med.* 2004 Apr 22;350(17):1710-2. PubMed PMID: 15102996.

## Links:

Faculty webpage: <http://sph.umd.edu/people/donald-milton>

CATCH-the virus study page: <https://catch.umd.edu/>

Google Scholar Profile: <https://scholar.google.com/citations?user=35qhH0QAAAJ&hl=en>

PHAB Lab page: <http://sph.umd.edu/laboratory-resources/public-health-aerobiology-virology-and-exhaled-biomarker-laboratory-phab-lab>

**Justin Ortiz** ([jortiz@som.umaryland.edu](mailto: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>

**Kari Ann Shirey** ([KShirey@som.umaryland.edu](mailto: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<sup>-/-</sup> 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- $\gamma$ - 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/](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:

Med School faculty page: <http://www.medschool.umaryland.edu/profiles/Vogel-Stefanie/>

PubMed publications:

<http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40447249/?sort=date&direction=ascending>