Respiratory Pathogens Research Center Symposium

Tuesday, May 15th, 2018

Saunders Research Building
University of Rochester Medical Center
Rochester, NY

About our program:

RESPIRATORY PATHOGENS RESEARCH CENTER (RPRC)

David J. Topham[1], PhD, Director
Ann Falsey[2], MD, Co-Director
[1]Center for Vaccine Biology and Immunology, Department of Microbiology and Immunology, University of Rochester Medical Center, Rochester, NY
[2]Infectious Disease Unit, Department of Medicine, University of Rochester Medical Center, Rochester, NY

The Respiratory Pathogens Research Center (RPRC) was created to develop new insight, tools, and strategies in order to decrease the significant global health burden caused by viruses and bacteria that take aim at the respiratory system. These pathogens cause pneumonia and flu, as well as other infections caused by lesser-known but still-deadly microbes such as coronaviruses, metapneumoviruses, parainfluenza viruses, and respiratory syncytial virus, as well as a host of bacteria.

The RPRC, which was established by the National Institute of Allergy and Infectious Diseases (NIAID) in 2011, consists of a national network of scientists focusing on research that will lead to a better understanding of the complex interactions between respiratory pathogens, the immune system, and other genetic and environmental factors and how these interactions can cause complications, and developing new ways to treat or prevent these diseases.

RESPIRATORY PATHOGENS RESEARCH CENTER SYMPOSIUM
Tuesday, May 15th, 2018. 7:45 a.m. – 6:00 p.m.
Saunders Research Building and Helen Wood Hall Auditorium

7:45 - 8:45 a.m.
REGISTRATION, Poster set-up, Continental Breakfast

8:45 - 9:00 a.m.,
David Topham and Ann Falsey - *WELCOME AND INTRODUCTION*

9:00 - 9:40 a.m.
OCTAVIO RAMILO, Nationwide Children's Hospital
The Infant Immune System in Infection and Vaccination

9:40 - 9:55 a.m.
SHORT TALK: **Janelle Veazey,** University of Rochester
Inhibiting Protein Kinase D3 Protects Against Viral Respiratory Infection by Altering Epithelial Antiviral and Pro-Inflammatory Responses

9:55 - 10:35 a.m.
THOMAS MARIANI, University of Rochester
Insufficiency in airway interferon activation defines clinical severity to infant RSV infection

10:35 - 10:50 a.m.
SHORT TALK: **Thomas Thatcher,** University of Rochester
Cigarette Smoke Increases Severity of Influenza A Viral Infection and Impairs Epithelial Antiviral Responses in a Mouse Model

10:50 - 11:20 a.m. Coffee Break

11:20 - 12:00 p.m.
HONGZHE LEE, University of Pennsylvania
Quantifying and Comparing Bacterial Growth Dynamics in Multiple Metagenomic Samples

12:00 – 12:15 p.m.
SHORT TALK: **Soumyaroop Bhattacharya,** University of Rochester
Identification and Replication of Transcriptomic Biomarkers of Bacterial Involvement in Lower Respiratory Tract Infections

12:15 – 12:55 p.m.
MELINDA PETTIGREW, Yale School of Public Health
Haemophilus influenzae and chronic obstructive pulmonary disease (COPD): Is persistence just a phase?

12:55 – 2:30 pm
LUNCH & POSTER VIEWING

2:30 – 3:10 p.m.
TINA HARTERT, Vanderbilt University
Asthma: The tale of an infectious etiology of a chronic disease

3:10 – 3:25 p.m.
SHORT TALK: **Xing Qiu,** University of Rochester
Development of Nasal Gene Expression-Based Predictors for Respiratory Disease Severity for Infant RSV Infection

3:25 – 4:05p.m.
STEVE VARGA, University of Iowa
Inflammasome Activation is Influenced by RSV Strain Differences

4:05 – 4:20 p.m.
SHORT TALK: **Andrew Dylag,** University of Rochester
Neonatal Hyperoxia Enhances Respiratory Syncytial Virus-Mediated Changes in Pulmonary Function and Alveolar Development in Mice

4:20 – 5:00 p.m.
KRISTIN SCHEIBLE, University of Rochester
Mapping pre- and post-natal T cell development and its impact on respiratory outcomes in premature and full term infants

5:00 – 6:00 p.m.
WINE AND CHEESE RECEPTION & POSTER VIEWING

9:00 - 9:40 a.m.

OCTAVIO RAMILO, MD

Henry G. Cramblett Chair in Infectious Diseases and Professor of Pediatrics,
Chief of Infectious Diseases,
Principal Investigator, Center for Vaccines and Immunity,
National Children's Hospital, Columbus, Ohio

The Infant Immune System in Infection and Vaccination

Octavio Ramilo is the Henry G. Cramblett Chair in Medicine and Professor of Pediatrics at the Ohio State University College of Medicine and Chief of the Division of Infectious Diseases at Nationwide Children's Hospital in Columbus, Ohio. He obtained his medical degree from the Universidad Complutense in Madrid, Spain. Dr. Ramilo completed his pediatric residency at the Hospital "12 de Octubre" in Madrid and a subsequent Pediatric Infectious Disease Fellowship at the University of Texas Southwestern Medical Center in Dallas, Texas.

He has been involved in translational and clinical research related to the role of the host immune response in pathogenesis of infectious diseases for over 25 years. His current research is focused on pathogenesis and treatment of respiratory infections, especially RSV, and the application of genomics and system analysis approaches for improving diagnosis and understanding of host responses to infectious agents and vaccines.

9:40 - 9:55 a.m.

SHORT TALK: **Janelle Veazey**, *Graduate Student, Dept. of Microbiology and Immunology, University of Rochester, Rochester, NY*

Inhibiting Protein Kinase D3 Protects Against Viral Respiratory Infection by Altering Epithelial Antiviral and Pro-Inflammatory Responses

Janelle Veazey[1], Timothy Chapman[2], Timothy Smyth[3], Sara Hillman[2], Zackery Knowlden[2], Sophia Eliseeva[2], Savas Hetelekides[2], Steve Georas[1,2]
Dept. of Microbiology and Immunology[1], Dept. of Pulmonary and Critical Care Medicine[2], Dept. of Environmental Medicine[3], University of Rochester, Rochester, NY.

Rationale: Protein kinase D (PKD) is a serine/threonine kinase family with three isoforms (PKD1-3), is expressed in many cell types and is implicated in cell growth, differentiation, ROS response and cytokine secretion. Previously, we have shown that the isoform PKD3 is highly expressed in airway epithelial cells and its inhibition promotes barrier integrity. We hypothesized that PKD3 regulates additional aspects of early innate immunity, and here demonstrate that PKD inhibition limits interferon (IFN) and pro-inflammatory cytokines levels while also restricting Influenza A viral burden, making PKD an attractive therapeutic target.

Methods: PKD signaling was blocked with the water-soluble competitive inhibitor CRT0066101 (CRT) in both 16HBE (human bronchial epithelial cell line) cells and in a murine model (oropharengeal treatment) prior to, and during, stimulation with viral mimetic dsRNA (polyI:C). IFN and cytokine levels were determined via ELISA/multiplex and mRNA levels via RT-PCR. Effects of PKD on viral level (RT-PCR of M protein) were tested by infecting A549 (human lower airway epithelial cell line) cells with Influenza A virus (PR/8 MOI 0.075) with/without CRT.

Results: PKD inhibition significantly reduced secreted IFN-lambda in 16HBE cells (22377 ±292pg/ml to 9612 ±2958pg/ml; $p<0.001$). Mechanistically, we found PKD inhibition reduced mRNA levels of IFN-alpha, IFN-lambda, and several pro-inflammatory cytokines/chemokines, including CXCL1, IL-6, TNF-alpha, and GM-CSF. Consistent with *in vitro* findings, CRT treatment reduced recovery of IFN-lambda (144 ±30pg/ml to 56 ±13pg/ml; $p<0.0001$) and several other pro-inflammatory mediators in bronchoalveolar lavage fluid (BALF) following polyI:C administration *in vivo*. Genetic deletion of PKD3 in particular reduced IFN-lambda (202 ±35pg/ml to 133 ±28pg/ml) and a wide array of pro-inflammatory cytokine/chemokines recovered in BALF, highlighting the role of PKD3 in regulating early innate immune signaling.

Intriguingly, the reduction in IFN signaling following CRT treatment did not result in elevated viral levels in Influenza A virus-infected A549 cells. In fact, viral mRNA was reduced in a dose-dependent manner with PKD inhibition. Current work looks to investigate the effect of PKD3 deficiency on influenza A infection/replication *in vivo*.

Conclusions: PKD3 promotes IFN and pro-inflammatory cytokine/chemokine production in the lung. Ongoing work looks to determine which pattern recognition receptor leads to PKD3 activation and to elucidate the molecular pathway PKD3 acts on to modulate cytokine mRNA levels. Importantly, our findings that PKD inhibition promotes barrier integrity, lowers pro-inflammatory cytokines while also restricting viral replication makes PKD an attractive target for novel therapeutics against a wide range of respiratory viruses.

Funding: The project described was supported by Award Number T32AI007285 from the National Institute of Allergy and Infectious Diseases, and R01 HL12424 from NIH/NHLBI.

9:55 - 10:35 a.m.

THOMAS MARIANI, **PhD**
Professor, Pediatrics & Neonatology,
University of Rochester, Rochester, NY

Insufficiency in airway interferon activation defines clinical severity to infant RSV infection

The broad objectives of the Mariani laboratory are to identify the mechanisms of susceptibility to lung diseases, particularly focusing upon their developmental antecedents and the influence of environmental factors. This involves defining key regulatory networks contributing to lung development and maturation, and which may be perturbed in diseased states such as asthma, chronic obstructive pulmonary disease (COPD) and bronchopulmonary dysplasia (BPD). An additional area of significant recent interest is in the characterization of host factors contributing to risk or severity of infant respiratory infections. The laboratory is recognized for its contributions to the application of genomics methods, both for defining developmental mechanisms and for disease gene discovery. Additionally, the laboratory utilizes state-of-the-art genetic modeling in animals, exposure-related models of chronic lung disease and studies of human samples.

Dr. Mariani is active in Departmental, professional society and conference organization leadership. In 2012, Dr. Mariani established the University of Rochester Program in Pediatric Molecular and Personalized Medicine and the Pediatric Translational Biospecimen Laboratory, to support and expand translational research consistent with the goals of the Department. He assumed the position of Vice Chair for Research in 2017. Dr. Mariani has, and continues to serve in multiple positions in the American Thoracic Society. He was Chair for the 2015 Gordon Conference on Lung Development, Injury and Repair. In addition, he has extensive experience with the review and evaluation of research, including a current term on the Lung Injury, Repair and Regeneration Scientific Review Group for the NIH.

10:35 - 10:50 a.m.

SHORT TALK: **Thomas Thatcher**, *Research Associate Professor, Dept. of Medicine/Pulmonary & Critical Care, University of Rochester, Rochester, NY*

Cigarette Smoke Increases Severity of Influenza A Viral Infection and Impairs Epithelial Antiviral Responses in a Mouse Model

Parker F. Duffney[1], Aitor Nogales[2], Thomas H. Thatcher[3], Luis Martinez-Sobrido[2], Richard P. Phipps[1,2,3,4], Patricia J. Sime[1,3,4]

[1] Department of Environmental Medicine, University of Rochester, Rochester, NY. [2] Department of Microbiology and Immunology, University of Rochester, Rochester, NY. [3] Lung Biology and Disease Program, University of Rochester, Rochester, NY. [4] Division of Pulmonary and Critical Care Medicine, University of Rochester Medical Center, Rochester, NY

Cigarette smokers have increased incidence of respiratory infections, which also can trigger exacerbations of underlying diseases such as chronic obstructive pulmonary disease. We have previously shown that cigarette smoke impairs anti-viral responses in small airway epithelial cells in culture. However, mouse models show increased inflammation and interferon (IFN) production in mice infected with influenza A virus (IAV) after exposure to cigarette smoke. We hypothesize that excessive inflammation in mouse models is due to impaired antiviral responses in lung epithelium, which results in increased viral spread.

Adult (6-to-8-week-old) C57BL/6 female mice were exposed to cigarette smoke 5 times a day for 5 weeks followed by infection with a replication competent mCherry-expressing fluorescent IAV (A/Puerto Rico/8/34 H1N1, PR8 mCherry). Daily smoke exposures were continued following infection, and the mice were sacrificed 2 and 4 days post-infection. Severity of infection was measured by monitoring weight loss during two weeks after PR8 mCherry infection. Viral spread was determined by fluorescent mCherry intensity measured by imaging whole lungs with an in vivo imaging system (IVIS) as well as assessing viral RNA levels. Cell differentials were performed from the broncho-alveolar lavage fluid (BALF) and RNA was isolated from lung tissue. mRNA levels of interferon β (beta), interferon λ (lambda) and CXCL1 determined by qRT-PCR. Separate lungs were fixed in formalin for histologic analysis. Mouse lung epithelial cells were isolated 3 days post infection by digesting lung tissue and removing CD45+ cells prior to positive selection for the epithelial cell marker CD326.

Smoke-exposed mice infected with PR8 mCherry IAV have increased lung inflammation including increases in polymorphonuclear cells in the BALF ($p<0.001$) and increased CXCL1, IFNλ (lambda), and IFNβ (beta) mRNA at both day 2 and day 4 post-infection. Smoke exposed mice also had increased

viral replication in the lungs, as determined by increased radiance efficiency of mCherry fluorescence in whole lungs and by elevated viral mRNA ($p<0.01$). Interestingly, CD45- CD326+ cells isolated from smoke exposed mice following PR8 mCherry infection had impaired production of IFNβ (beta) and CXCL1 mRNA ($p<0.05$) while CD45+ cells did not.

Prior cigarette smoke exposure impairs lung epithelial innate responses to IAV, leading to increased viral load, greater recruitment of inflammatory cells, and ultimately enhanced inflammation. Antiviral responses were suppressed in resident lung epithelium but not recruited inflammatory leukocytes. Specifically targeting the impairments in the lung epithelium can serve as a therapeutic target for those at high risk for CODP exacerbations.

11:20 - 12:00 p.m.

HONGZHE LEE, **PhD**
Professor of Biostatistics in Biostatistics and Epidemiology
University of Pennsylvania, Philadelphia, PA

Quantifying and Comparing Bacterial Growth Dynamics in Multiple Metagenomic Samples

Dr. Hongzhe Li is a Professor of Biostatistics and Statistics at the Perelman School of Medicine at the University of Pennsylvania (Penn). He is the Chair of the Graduate Program in Biostatistics and Director of Center of Statistics in Big Data at Penn. Dr. Li has been elected as a Fellow of the American Statistical Association (ASA), a Fellow of the Institute of Mathematical Statistics (IMS) and a Fellow of AAAS. Dr. Li severed on the Board of Scientific Counselors of the National Cancer Institute of NIH and regularly serves on various NIH study sections. He is currently an Associate Editor of Biometrics, Statistica Sinica and also co-Editor-in-Chief of Statistics in Biosciences. He serves as Chair of the Section on Statistics in Genomics and Genetics of the ASA. Dr. Li's research has been focused on developing powerful statistical and computational methods for analysis of large-scale genetic, genomics and metagenomics data and high dimensional statistics with applications in genomics. He has published papers in Science, Nature, Nature Genetics, Science Translational Medicine, JASA, JRSS, Biometrika, etc.

12:00 – 12:15 p.m.

SHORT TALK: **Soumyaroop Bhattacharya,** *Senior Associate, Pediatrics M&D Neonatology, University of Rochester, Rochester, NY*

Identification and Replication of Transcriptomic Biomarkers of Bacterial Involvement in Lower Respiratory Tract Infections

[1]Soumyaroop Bhattacharya, [2]Alex Rosenberg, [3]Derick Peterson, [3]Katherine Grzesik, [3]Andrea Baran, [4]John Ashton, [4]Steven Gill, [3]Anthony Corbett, [3]Jean Holden-Wiltse, [5]Edward Walsh, [1]Thomas Mariani and [5]Ann Falsey
[1]Division of Neonatology, Department of Pediatrics, [2]Division of Allergy Immunology & Rheumatology, Department of Medicine, [3]Department of Biostatistics and Computational Biology, [4]Genomics Research Center, and [5]Division of Infectious Diseases, Department of Medicine University of Rochester, Rochester, NY.

Rationale: Lower respiratory tract infections (LRTIs) are common causes of hospitalization in adults, and can be due to viruses and/or bacteria. Because it is challenging to accurately determine the cause of infection with current diagnostic tests, antibiotics are nearly always prescribed, even when unnecessary. We undertook the current study to rigorously assess the value of peripheral blood gene expression to identify subjects with bacterial involvement in LRTI. Prior work suggests that gene expression patterns in peripheral blood can provide useful diagnostic information.

Methods: 213 hospitalized subjects >18 years of age consented to participate in the study. Clinical data and peripheral blood RNA was collected, and comprehensive microbiologic testing was performed. Using stringent criteria 98 subjects could be classified as: absence of bacterial infection, N=55 (viral infection alone) or presence of bacterial infection, N=43 (28 bacterial alone and 15 mixed viral-bacterial infection). Gene expression analysis was performed using RNASeq and quantitative real-time PCR (qPCR). Univariate gene selection and screening was based on the Bonferroni-corrected Wilcoxon test. Constrained logistic models to predict bacterial infection were fit using screened LASSO and supervised principal components analysis. Cross-validated (CV) AUC was used to select the screening level and LASSO penalty, and the entire procedure was nested within an outer CV loop to estimate the AUC of the adaptive procedures.

Results: RNAseq analysis identified 249 genes differentially expressed in LRTI subjects with bacterial infection, whether viral co-infection was present or absent. These genes implicated the involvement of obvious infection-related (e.g. viral infection, viral replication), as well as novel (e.g. cell phagocytosis, neuromuscular disease), pathways. Interestingly, subjects with co-

infection (bacterial plus viral) displayed a transcriptomic profile more similar to those with a bacterial infection alone. Importantly, while selected clinical variables (BUN, WBC, infiltrates, congestion) were capable of discriminating between bacterial and non-bacterial LRTI with surprisingly high accuracy (AUC=0.81), gene expression patterns performed as well as clinical variables. A 10 gene set demonstrated the highest predictive accuracy for bacterial LRTI (AUC=0.84) in the absence of clinical information. Using qPCR, we replicated differential expression of genes previously shown to discriminate subjects with bacterial and non-bacterial LRTI (Suarez et al., 2015), and validated novel predictors of bacterial involvement identified in our studies (IF127, SIGLEC10, LTA4H).

Summary: Our data strongly suggest that host peripheral blood gene expression patterns can be informative in the diagnosis of bacterial infection in LRTI.

Funding: HHSN272201200005C (RPRC)

12:15 – 12:55 p.m.

MEINDA PETTIGREW, PhD

Senior Associate Dean of Academic Affairs and Professor of Epidemiology,
Yale School of Public Health, New Haven, CT

Haemophilus influenzae and chronic obstructive pulmonary disease (COPD): Is persistence just a phase?

Melinda Pettigrew, PhD is a Professor of Epidemiology in the Department of Epidemiology of Microbial Diseases and the Senior Associate Dean for Academic Affairs at the Yale School of Public Health. Professor Pettigrew's research focuses on pathobionts of the respiratory tract (e.g., *Haemophilus influenzae* and *Streptococcus pneumoniae*) and the growing public health threat of antibiotic resistance. Current projects utilize next-generation sequence technologies to identify factors that influence bacterial persistence and whether pathobionts asymptomatically colonize or cause diseases such as pneumonia and exacerbations of chronic obstructive pulmonary disease (COPD). Professor Pettigrew serves on the Steering Committee of the Antibiotic Resistance Leadership Group and on the editorial boards of *mBio* and the *Journal of Clinical Microbiology*.

2:30 – 3:10 p.m.

TINA HARTERT, MD, MPH

Professor of Medicine; Assistant Vice President for Clinical Translational Science; Director, Center for Asthma Research
Vanderbilt University, Nashville, TN

Asthma: The tale of an infectious etiology of a chronic disease

Dr. Hartert is an internationally recognized scientist whose focus is in primary and secondary prevention of asthma through identification of risk factors and understanding of the pathways through which they contribute to asthma development. She is the Director of the Center for Asthma Research, a highly multidisciplinary translational research group including investigators in psychology, genetics, geography, economics, virology, biostatistics, epidemiology, and public health. The group's focus is the discovery, understanding and implementation of primary and secondary disease prevention strategies for asthma and allergic diseases. In addition, the group has a heavy focus on research mentoring and the development of the next generation of translational investigators. Dr. Hartert's group has advanced our understanding of the clinical significance of respiratory infections and oxidant defense in the development of asthma, as well as establishing evidence for the causal role of respiratory viral infection in asthma development. In addition her collaborative work has established asthma and allergic diseases as risk factors for vaccine preventable diseases, work that has led to new vaccine recommendations for both influenza vaccination during pregnancy and pneumococcal vaccination among asthmatics. Her research contributions have been recognized by election to the American Society of Clinical Investigation (ASCI) and Association of American Physicians (AAP), and she recently completed service as an Associate Editor of the *American Journal of Respiratory and Critical Care Medicine*. In addition, she has served as a member of a number of NIH expert panels establishing disease guidelines and research agendas, and as standing member of study sections. She has worked internationally and domestically with academic, clinical and industry partners, and has established one of the largest group of birth cohorts for the study of asthma and allergic diseases in the world. She has been continuously funded by the NIH since 1999, and is additionally supported by an NIH mid-career award to protect time for mentoring. She is most proud of the many fellows and students whom she has mentored and who have published over 150 first author manuscripts and abstracts. In 2015 she was awarded the inaugural Vanderbilt award in research mentoring of clinical-translational scientists.

3:10 – 3:25 p.m.

SHORT TALK: **Xing Qiu,** *Associate Professor, Biostatistics Computational Biology, University of Rochester, Rochester, NY*

Development of Nasal Gene Expression-Based Predictors for Respiratory Disease Severity for Infant RSV Infection

Xing Qiu[1], Thomas J. Mariani[2], Lu Wang[1], ChinYi Chu[3], Juilee Thakar[4], Matthew McCall[1], Alex Grier[5], Steven Gill[4], Jeanne Holden-Wiltse[1], Anthony Corbett[6], David J. Topham[4], Ann R. Falsey[7], Mary T. Caserta[8], and Edward E. Walsh[7]

[1]Biostats Computational Biology, [2]Department of Pediatrics – Neonatology, [3]Ctr Pediatric Biomed Research, [4]Microbiology and Immunology, [5] Functional Genomics, [6] Clin & Trans Science Institute, [7]Medicine M&D-Infect Dis Unit, [8]Pediatrics M&D Inf Diseases, University of Rochester, Rochester, NY

Abstract: In this study, we developed two nasal gene expression-based severity scores (NGSS1 and NGSS2) that have strong correlation with the clinically defined Global Respiratory Severity Score (GRSS). Specifically, we collect 200 nasal gene expression profiles from 125 RSV infected subjects at two time points: (a) Visit 1, which is the acute infection stage (~4 days since disease onset; 106 samples), and (b) Visit 2, the convalescence stage (~4 weeks since disease onset; 69 samples). All subjects are assigned with the GRSS measured at the acute infection stage. After preprocessing, marginal screening, and model selection, we built two sparse linear predictor of GRSS: (a) NGSS1 is a function of 41 genes that has the best cross-validated prediction accuracy, and (b) NGSS2 is a function of 35 stable genes, defined as those genes that has less than 10% and statistically insignificant ($p>0.5$ in paired t-tests) up- or down-regulation between Visits 1 and 2. We found that NGSS1 correlated with the GRSS very well (naïve correction: $\rho=0.935$; cross-validated correlation: $\rho=0.813$). Besides, when used as a binary classifier (mild versus severe), NGSS1 correctly identified 89.6% of the symptom severity in in cross-validation studies. Compared with NGSS1, NGSS2 had slightly less but comparable prediction accuracy: naïve correction: $\rho=0.885$; cross-validated correlation: $\rho=0.723$; cross-validated classification accuracy: 83.0%). Due to the use of stable genes in NGSS2, we hypothesize that NGSS2 may have potential to be used as a prognostic biomarker for respiratory disease severity prior to infant RSV infections.

3:25 – 4:05 p.m.

STEVE VARGA, PhD

Professor of Microbiology and Immunology,
Professor of Pathology,
Director, Interdisciplinary Graduate Program in Immunology
University of Iowa, Iowa City, IA

Inflammasome Activation is Influenced by RSV Strain Differences

Dr. Varga is a Professor in the Department of Microbiology and Immunology at the University of Iowa. Dr. Varga also serves as Director of the Interdisciplinary Graduate Program in Immunology. Dr. Varga serves on several journal editorial boards including the Journal of Immunology, the Journal of Virology and PLoS ONE and was a co-organizer of the 8th International RSV Symposium held in Santa Fe, NM in 2012. Dr. Varga is a member of the Education Committee for the American Association of Immunologists and serves as the Coordinator for the Grant Review for Immunologists Program (GRIP).

Dr. Varga received his Ph.D in Immunology and Virology from the University of Massachusetts Medical Center in 1999. He served as a post-doc at the University of Virginia from 1999-2003. The Varga laboratory focuses on the role of virus-specific T lymphocytes in contributing to enhanced disease and immunopathology during respiratory viral infections. A major focus of the laboratory is gaining a better understanding of the immune response to respiratory syncytial virus (RSV) infection.

4:05 – 4:20 p.m.

SHORT TALK: **Andrew Dylag, Assistant** *Professor of Pediatrics, Division of Neonatology, University of Rochester, Rochester, NY*

Neonatal Hyperoxia Enhances Respiratory Syncytial Virus-Mediated Changes in Pulmonary Function and Alveolar Development in Mice

Andrew M. Dylag MD[1], Jeannie Haak MS[1], William Domm PhD[1,2], Min Yee1, and Michael A. O'Reilly PhD[1,2]

[1]Department of Pediatrics and [2]Environmental Medicine, University of Rochester Medical Center, Rochester, NY.

Background: Children who develop early respiratory syncytial virus infections (RSV) are at risk for wheezing disorders later in life. Those children who were born preterm and experience neonatal oxygen exposure often experience worse respiratory morbidity and pulmonary function following an RSV infection than term infants. We developed a novel mouse model of combined neonatal hyperoxia and subsequent RSV infections to determine their influence on pulmonary function, airway and alveolar structure, and smooth muscle hypertrophy.

Design/Methods: Newborn C57BL/6J pups were placed in 100% oxygen (O2) or room air (RA) between postnatal days 0-4. Pups were infected with 10E7 plaque forming units of Human A2 RSV or PBS (Sham) on postnatal day 5. Changes in inflammatory cytokines/chemokines were evaluated by real-time PCR at 2, 4, and 6 days post-infection. Baseline pulmonary function and methacholine-induced airway hyperreactivity were assessed with a small-animal ventilator (FlexiVent, SCIREQ, Montreal, Canada) at 4 (P28) and 8 (P56) weeks of age. Airway smooth muscle staining was quantified by counting positive cells using ImageJ software (NIH). Alveolar size was quantified by measuring the mean linear intercept.

Results: Minimal mortality was seen in mice exposed to neonatal hyperoxia and/or infected with RSV. Neonatal hyperoxia did not significantly influence expression of inflammatory genes (IL-13, IL-25, IL-33) that were elevated on post-infection days 2, 4, and 6. However, at 4 weeks of age, baseline respiratory mechanics defined by increased resistance, increased tissue damping, increased elastance, and decreased compliance was observed in O2-RSV animals compared to O2-sham animals. Several of these changes persisted at 8 weeks of age and were associated with more pronounced alveolar simplification with at least 15% less alveolar airspace compared to known alveolar changes seen in O2-sham mice. RA-RSV animals had increased staining for alpha smooth muscle actin correlating with a modest increase in baseline airway resistance.

Conclusions: Combined exposure to neonatal O2 and early RSV infection has a worsened effect on baseline respiratory mechanics and lung simplification than O2 or RSV alone, changes that persist into adulthood. These deviations may reflect a continued progression of the physiologic phenotype of infants with bronchopulmonary dysplasia or the early development of chronic obstructive pulmonary disease.

4:20 – 5:00 p.m.

KRISTIN SCHEIBLE, MD
Assistant Professor, Department of Pediatrics, Neonatology,
University of Rochester, Rochester, NY

Mapping pre- and post-natal T cell development and its impact on respiratory outcomes in premature and full term infants

Dr. Kristin Scheible completed her clinical training in Neonatology at the University of Rochester. She began her Immunology research during Fellowship in the laboratory of Dr. David Topham, focusing on human T cell responses to influenza infection. After Fellowship she applied her training in adult human immunology to begin her career investigating developmentally-determined T cell intrinsic differences in premature infants. The overall goal of her research program is to reveal molecular features specific to the developing adaptive immune system that can be targeted to improve respiratory outcomes (infectious and inflammatory) in premature infants. She leads several teams investigating human infant immunity, including the Prematurity, Respiratory, Immune System and Microbiome study (PRISM), the Environmental influences in Child Health Outcomes (ECHO) and Neoimmune (Blantyre, Malawi birth cohort). Dr. Scheible's teams deploy cutting-edge assay and analytic techniques to maximize gain from limited samples collected in neonates.

POSTERS

Presenter(s) listed BOLD

1	MECHANISMS OF RSV ATTACHMENT AND INFECTION OF A PHYSIOLOGICAL MODEL OF HUMAN PEDIATRIC LUNG EPITHELIAL CELLS **Christopher S. Anderson[1,2]**, Chin-Yi Chu[1,2], Jared Mereness[1,2], Qian Wang[1,2], Ravi S Misra[1], Stephen Romas[1], Heidie Huyck[1], Amanda Howell[1], Gautam Bandyopadhyay[1], Gloria S. Pryhuber[1] and Thomas J. Mariani[1,2] [1]Division of Neonatology and [2]Program in Pediatric Molecular and Personalized Medicine, Department of Pediatrics, University of Rochester Medical Center, Rochester NY
2	DEVELOPMENT OF A COMPUTATIONAL ALGORITHM FOR THE CURATION, INFERENCE, AND ANALYSIS OF VIRAL RESPONSIVE GENE-SETS **Lauren Benoodt[1]**, Lu Wang[3], Jeanne Holden-Wiltse[3], Anthony Corbett[3], Ann R Falsey[5], Mary T. Castera[4], Thomas J. Mariani[6,4], Xing Qiu[3], David J. Topham[2], Edward E Walsh[5], and Juilee Thakar[1,2,3] *[1]Department of Biochemistry and Biophysics, [2]Department of Microbiology and Immunology, [3]Department of Biostatistics and Computational Biology, [4]Department of Pediatrics, [5]Department of Medicine and Infectious Diseases, [6]Department of Biomedical Genetics, University of Rochester, Rochester NY*
3	IDENTIFICATION AND REPLICATION OF TRANSCRIPTOMIC BIOMARKERS OF BACTERIAL INVOLVEMENT IN LOWER RESPIRATORY TRACT INFECTIONS **[1]Soumyaroop Bhattacharya**, [2]Alex Rosenberg, [3]Derick Peterson, [3]Katherine Grzesik, [3]Andrea Baran, [4]John Ashton, [4]Steven Gill, [3]Anthony Corbett, [3]Jean Holden-Wiltse, [5]Edward Walsh, [1]Thomas Mariani and [5]Ann Falsey *[1] Department of Pediatrics – Neonatology [2]Division of Allergy Immunology & Rheumatology, Department of Medicine, [3]Department of Biostatistics and Computational Biology, [4]Genomics Research Center, and [54]Department of Medicine -Infect Dis Unit, University of Rochester, Rochester, NY*
4	SYSTEMATIC STUDY OF INFLUENZA A AND B VIRUS CO-INFECTIONS **Pilar Blanco-Lobo**, Laura Rodriguez, Aitor Nogales, Luis Martinez-Sobrido *Department of Microbiology and Immunology, University of Rochester, Rochester, NY*

5	INCIDENCE AND EVALUATION OF THE CHANGE IN FUNCTIONAL STATUS ASSOCIATED WITH RESPIRATORY SYNCYTIAL VIRUS INFECTION IN HOSPITALIZED OLDER ADULTS **Angela Branche, MD[1],** Evelyn Granieri MD, MPH[2], Edward Walsh, MD[1,3] Lynn Finelli, DrPH, MS[4], Falsey, MD[1,3], , William G. Greendyke, MD[2,5], Angela E. Barrett, BA[5], Celibell Y. Vargas, MD[5,6], Lisa Saiman, MD, MPH[5,6] *[1]Department of Medicine -Infect Dis Unit, University of Rochester, Rochester, NY. [2]Department of Medicine, Columbia University of Medical Center, New York, NY. [3]Rochester General Hospital, University of Rochester, Rochester,* NY. *[4]Center for Observational and Real-World Evidence, Merck & Co., Inc., Kenilworth, NJ. [5]Department of Infection Prevention and Control, New York-Presbyterian Hospital, New York, NY. [6]Department of Pediatrics, Columbia University Medical Center, New York, NY*
6	DEVELOPMENTAL ACTIVATION OF THE ARYL HYDROCARBON RECEPTOR DURABLY ALTERS CELLULAR PROCESSES CRITICAL FOR CD4+ T CELL FUNCTION **Catherine G. Burke[1]**, Jason R. Myers[2], Lisbeth A. Boule[1], and B. Paige Lawrence[1,3] *Department of [1]Microbiology and Immunology, [2]Genomics Research Center, and [3]Department of Environmental Medicine, University of Rochester Medical Center, Rochester, NY*
7	RSV DISEASE SEVERITY IS ENHANCED IN INFANTS WITH PRIOR COLONIZATION WITH H. INFLUENZAE **Mary T. Caserta[1],** Hongmei Yang[2], Sanjukta Bandopadhyay[2], Alex Grier[3], Xing Qiu[2], Andrew McDavid[2], Kristin Scheible[1], Steven Gill[3], and Gloria Pryhuber[1] *Department of Pediatrics[1], Biostatistics and Computational Biology[2], and Microbiology and Immunology[3], University of Rochester Medical Center, Rochester, NY*
8	THE RESPIRATORY MICROBIOTA BEFORE, DURING, AND AFTER RESPIRATORY SYNCYTIAL VIRUS (RSV) INFECTION. Alex Grier[2], Steven Gill[1], Matthew McCall[2], James Java[2], Xing Qiu[2], Lu Wang[2], Anthony Corbett[2], **Mary Caserta[3]**, Edward Walsh[4] *Department Microbiology and Immunology[1], Biostatistics and Computational Biology[2], Pediatrics[3] and Medicine[4]. University of Rochester Medical Center, Rochester, NY*

9	DETECTION AND CHARACTERIZATION OF HEMAGGLUTININ-SPECIFIC ANTIBODY-SECRETING CELLS BY FLOW CYTOMETRY WITH TETRAMERIC PROBES **Francisco A. Chaves,** Marta L. DeDiego, Nathan Laniewski, Phuong Nguyen, Mark Y. Sangster and David J. Topham. *Center for Vaccine Biology and Immunology, Department of Microbiology and Immunology, University of Rochester Medical Center, Rochester, NY*
10	AIRWAY GENE EXPRESSION CORRELATES OF CLINICAL SEVERITY FOLLOWING RESPIRATORY SYNCYTIAL VIRUS INFECTION IN INFANTS **Chin-Yi Chu[1]**, Xing Qiu[2], Lu Wang[2], Brenda Tesini[3], Jeanne Holden-Wiltse[2], David J. Topham[4], Ann R. Falsey[3], Mary T. Caserta[5], Edward E. Walsh[3], and Thomas J Mariani[1] *[1]Departments of Pediatrics - Ctr Pediatric Biomed Research, [2]Department of Biostatistics and Computational Biology, [3] Department of Medicine -Infect Dis Unit, Medicine, [4] Center for Vaccine Biology and Immunology, Department of Microbiology and Immunology,[5] Department of Pediatrics M&D – Inf Diseases, University of Rochester, Rochester, NY*
11	NEONATAL HYPEROXIA ENHANCES RESPIRATORY SYNCYTIAL VIRUS-MEDIATED CHANGES IN PULMONARY FUNCTION AND ALVEOLAR DEVELOPMENT IN MICE **Andrew M. Dylag MD[1]**, Jeannie Haak MS[1], William Domm PhD[1,2], Min Yee[1], and Michael A. O'Reilly PhD[1,2] *[1]Department of Pediatrics and [2]Environmental Medicine, University of Rochester Medical Center, Rochester, NY*
12	NEONATAL GUT AND RESPIRATORY MICROBIOTA: COORDINATED DEVELOPMENT THROUGH TIME AND SPACE Alex Grier[1], Andrew McDavid[2,], Bokai Wang[2] , Xing Qiu[2], James Java[2], Sanjukta Bandyopadhyay[2], Hongmei Yang[2],Jeanne Holden-Wiltse[2,] Haeja A. Kessler[3], Ann L. Gill[3], Heidie Huyck[4], Ann R. Falsey[4], David J. Topham[3,5], Kristin M. Scheible[6], Mary T. Caserta[7], Gloria S. Pryhuber[6], and **Steven R. Gill1,[3]** University of Rochester School of Medicine and Dentistry, Rochester, NY, USA: [1]Genomics Research Center; [2]Department of Biostatistics and Computational Biology; [3]Department of Microbiology and Immunology; [4]Medicine-Infectious Disease; [5]Center for Vaccine Biology and Immunology; [6]Division of Neonatology, Department of Pediatrics; [7]Division of Infectious Disease, Department of Pediatrics

13	DATA INTEGRATION, VISUALIZATION AND REPRODUCIBLE ANALYSIS WITH THE BIO-LAB INFORMATICS SERVER Anthony Corbett, Jennifer Dutra, Andy Straw, Alicia Tyrell, Cameron Baker, Jeffrey Williams, **Jeanne Holden-Wiltse** *Research Data Integration and Analytics Group, Department of Biostatistics and Computational Biology and Clinical and Translational Science Institute, University of Rochester Medical Center, Rochester, NY*
14	PERTUSSIS TOXIN TREATMENT SUGGESTS CD8+ T CELLS NEED CHEMOKINE SIGNALS TO LOCATE ANTIGEN-BEARING CELLS DURING INFLUENZA INFECTION **Kris Lambert**, Emma C. Reilly and David J. Topham *David H. Smith Center for Vaccine Biology & Immunology, Department of Microbiology & Immunology, University of Rochester Medical Center, Rochester, NY*
15	ANALYSIS OF SINGLE CELL EXPERIMENTS THAT REPEATEDLY MEASURE HUMAN POPULATIONS **Andrew McDavid**[1], Lynn Linn[2], Nathan Laniewski[3] and Kristin Scheible[4] *[1]Department of Biostatistics, [3]Microbiology and Immunology, and [4]Pediatrics University of Rochester, Rochester, NY; [2]Department of Statistics, Pennsylvania State University, State College, PA*
16	INTERPLAY OF PA-X AND NS1 PROTEINS IN REPLICATION AND PATHOGENESIS OF A TEMPERATURE-SENSITIVE 2009 PANDEMIC H1N1 INFLUENZA A VIRUS **Aitor Nogales**,[a] Laura Rodriguez,[a] Marta L. DeDiego,[a,b] David J. Topham,[a,b] Luis Martínez Sobrido[a] *Department of Microbiology and Immunology[a] and David Smith Center for Immunology and Vaccine Biology,[b] University of Rochester, Rochester, NY*
17	THE K186E AMINO ACID SUBSTITUTION IN THE CANINE INFLUENZA VIRUS H3N8 NS1 PROTEIN RESTORES ITS ABILITY TO INHIBIT HOST GENE EXPRESSION **Aitor Nogales,[a]** Caroline Chauché,[b] Marta L. DeDiego,[a,c] David J. Topham,[a,c] Colin R. Parrish,[d] Pablo R. Murcia,[b] Luis Martínez-Sobrido[a] *Department of Microbiology and Immunology, University of Rochester, Rochester, NY[a] ; MRC-University of Glasgow Centre for Virus Research, Glasgow, United Kingdom[b]; David Smith Center for Immunology and Vaccine Biology, University of Rochester, Rochester, NY[c] ; Baker Institute for Animal Health, College of Veterinary Medicine, Cornell University, Ithaca, NY[d]*

18	CD49a AND CD103 DISPLAY DIFFERENTIAL ROLES IN MOTILITY OF CD8+ T CELLS AFTER ACUTE INFLUENZA VIRUS INFECTION **Emma C Reilly[1]**, Kris Lambert[1], Aitor Nogales[2], Luis Martinez-Sobrido[2], and David J Topham[1] *[1]Center for Vaccine Biology and Immunology, [2]Department of Microbiology and Immunology, University of Rochester Medical Center, Rochester, NY*
19	LOWER RHINOVIRUS INFECTION RATE BUT HIGHER ILLNESS SEVERITY ARE PREDICTED BY IL8- PRODUCING T CELLS IN PRETERM AND FULLTERM INFANTS **Scheible, Kristin[1]**; Laniewski, Nathan[2]; Emo, Jason[1]; Yang, Hongmei[3]; Bandyopadhyay, Sanjukta[3];Holden-Wiltse, Jeanne[3]; Falsey, Ann[4]; Grier, Alex[5]; McDavid, Andrew[3]; Topham, David[2]; Gill,Steven[6]; Caserta, Mary[7]; Pryhuber, Gloria[1] *[1]Department of Pediatrics M&D - Neonatology, [2] David H. Smith Center for Vaccine Biology and Immunology, [3]Biostats Computational Biology, [4]Department of Medicine M&D-Infect Dis Unit, [5]Functional Genomics, [6] Department of Microbiology and Immunology, [7]Department of Pediatrics M&D – Inf Diseases, University of Rochester, Rochester, NY*
20	STATISTICAL APPROACHES TO DECREASING THE DISCREPANCY OF NON-DETECTS IN QPCR DATA **Valeriia Sherina**, Helene McMurray, Winslow Powers, Hartmut Land, Tanzy M.T. Love, Matthew N. McCall *University of Rochester Medical Center, Rochester, NY*
21	CIGARETTE SMOKE INCREASES SEVERITY OF INFLUENZA A VIRAL INFECTION AND IMPAIRS EPITHELIAL ANTIVIRAL RESPONSES IN A MOUSE MODEL Parker F. Duffney[1], Aitor Nogales[2], **Thomas H. Thatcher[3]**, Luis Martinez-Sobrido[2], Richard P. Phipps[1234], Patricia J. Sime[134] *[1]Department of Environmental Medicine, University of Rochester, Rochester, New York , [2]Department of Microbiology and Immunology, University of Rochester, Rochester, New York , [3]Lung Biology and Disease Program, University of Rochester, Rochester, New York , [4]Division of Pulmonary and Critical Care Medicine, University of Rochester Medical Center, Rochester, NY*

22	INHIBITING PROTEIN KINASE D3 PROTECTS AGAINST VIRAL RESPIRATORY INFECTION BY ALTERING EPITHELIAL ANTIVIRAL AND PRO-INFLAMMATORY RESPONSES **Janelle Veazey[1]**, Timothy Chapman[2], Timothy Smyth[3], Sara Hillman[2], Zackery Knowlden[2], Sophia Eliseeva[2], Savas Hetelekides[2], Steve Georas[1,2] *Department of Microbiology and Immunology[1], Department of Pulmonary and Critical Care Medicine[2], Department of Environmental Medicine[3], University of Rochester, Rochester NY*
23	AIMS, STUDY DESIGN AND ENROLLMENT RESULTS FROM THE ASSESSING PREDICTORS OF INFANT RESPIRATORY SYNCYTIAL VIRUS (RSV) EFFECTS AND SEVERITY (AsPIRES) STUDY. **Edward E. Walsh[1,7]**, Thomas J. Mariani[2,6], ChinYi Chu[2,6], Alex Grier[3,5], Steven Gill[3,5], Xing Qiu[4], Lu Wang[4], Jeanne Holden-Wiltse[4], Anthony Corbett[4], Juilee Thakar[4,5], Lauren Benoodt[5], Matthew McCall[4], David J. Topham[5], Ann R. Falsey[1,7], and Mary Caserta[6]. *[1]Department of Medicine, [2]Department of Pediatrics and Division of Neonatology and Pediatric Molecular and Personalized Medicine Program, [3]Genomics Research Center, [4]Department of Biostatistics and Computational Biology, [5]Department of Microbiology and Immunology, [6]Department of Pediatrics, University of Rochester Medical Center, Rochester, NY, and [7]Department of Medicine Rochester General Hospital, Rochester NY*
24	COMPLETE CHARACTERIZATION OF A NOVEL IN VITRO MODEL FOR HUMAN PEDIATRIC LUNG EPITHELIAL CELLS. **Qian Wang[1]**, Soumyaroop Bhattacharya[1], Jared Mereness[1,2,] Jacquelyn Lillis[4,5], Ravi S Misra[1], Stephen Romas[1], Heidie Huyck[1], Amanda Howell[1], Gautam Bandyopadhyay[1], Kathy Donlon[1], Jason R Myers[5], John Ashton[5], Gloria S. Pryhuber[1], Thomas J. Mariani[1,2,3] *[1]Division of Neonatology and Program in Pediatric Molecular and Personalized Medicine, Department of Pediatrics, [2]Department of Biomedical Genetics, and [3]Department of Environmental Medicine, [4]Center for Pediatric Biomedical Research [5]UR Genomics Research Center, University of Rochester Medical Center, Rochester NY*

25	ATAXIA-TELANGIECTASIA MUTATED IS REQUIRED FOR PROPER EPITHELIAL REPAIR AND IMMUNE REGULATION FOLLOWING INFLUENZA A VIRUS INFECTIONS **Rachel Warren[1]**, William Domm[2], Min Yee[2], Andrew Campbell[3], Jane Malone[2], Terry Wright[2], Margot Mayer-Proschel[3], and Michael A. O'Reilly[2] *Departments of Microbiology and Immunology[1], Pediatrics[2], and Biomedical Genetics[3] University of Rochester, Rochester, NY*
26	DEVELOPMENT OF A GROWTH REFERENCE TOOL USING FENTON DATA & WHO DATA FOR PREMATURE INFANTS Sanjukta Bandyopadhyay[1], Kristin M. Scheible[2], Mary T. Caserta[3], Gloria S. Pryhuber[2], Xing Qiu[1], Ann Falsey[4], David J. Topham[5], **Hongmei Yang[1]** *[1]Biostats Computational Biology, [2]Department of Pediatrics M&D – Neonatology, [3]Department of Pediatrics M&D – Inf Diseases, [4]Department of Medicine M&D-Infect Dis Unit, [5]Center for Vaccine Biology and Immunology, University of Rochester Medical Center, Rochester, NY*
27	SEVERITY OF TYPE II CELL DEPLETION INFLUENCES RECRUITMENT OF OTHER STEM CELL NICHES DURING ALVEOLAR REPAIR **Min Yee[1]**, William Domm[2], Matthew Kottman[3], Patricia Sime[3] B. Paige Lawrence[2], Michael A. O'Reilly[1] [1]Department of Pediatrics, [2]Department of Environmental Medicine, [3]Department of Medicine, School of Medicine and Dentistry The University of Rochester, Rochester NY
28	A LABEL-FREE OPTICAL BIOSENSOR FOR INFLUENZA VIRUS SEROTYPING AND EVOLUTIONARY ANALYSIS **Hanyuan Zhang[1,2]**, Carole Henry Dunand[4], Aitor Nogales[3], Chris Anderson[3], David Topham[3], Luis Martinez-Sobrido[3], Patrick Wilson[4], and Benjamin L. Miller[1,2] *Departments of [1]Dermatology, [3]Microbiology and Immunology, and [2]Materials Science Program, University of Rochester, Rochester, NY [4]Department of Medicine, University of Chicago, Chicago, Illinois*

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Thank you for your participation!

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