BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Schlesinger, Larry S.	Professor of Medicine
eRA COMMONS USER NAME Schl15	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	MM/YYYY	FIELD OF STUDY
Cornell University, Ithaca, NY	BA	06/1978	Biology
Rutgers Medical School	MD	06/1982	Medicine

A. Personal Statement

I am the Samuel Saslaw Professor of Medicine at The Ohio State University, first chair of the Department of Microbial Infection and Immunity, College of Medicine and founding Director of the OSU Center for Microbial Interface Biology (CMIB, (cmib.osu.edu), an interdisciplinary campus-wide program that focuses on infectious diseases of major concern to human health. I am an internationally recognized physician scientist in the pathogenesis of tuberculosis and diseases due to other intracellular pathogens that subvert lung immune mechanisms. I have been continuously funded by the NIH and a number of other agencies for over 25 years, am/have been a member or chair of several NIH study sections (current council member for NIAID) and other private and federal agencies, am a Fellow of the AAAS and American Academy of Microbiology, and am OSU's 2011 Distinguished Scholar and College of Medicine's 2015 Distinguished Professor. My laboratory has studied mammalian cell biology and immunology in great detail with a wide array of established methods and techniques with respect to bacterial pathogens, phagocytes and non-phagocytic cells. I have made major contributions in the areas of human innate immune recognition by PRRs (esp. C-type lectins such as CD206 and CD209, and TLRs) and phagocytic receptors, phagocytosis, intracellular trafficking, mycobacterial glycolipids in pathogenesis and host adaptation, and the role of surfactant in lung innate immunity for infectious agents. I have been working in the field of macrophage microRNA (miRNA) biology for the past 4 years and published the first paper (PNAS) in the field on the role of miRNAs in regulating the immunobiology of human macrophages in response to *M. tuberculosis* and linking their regulation to virulence. I have also been exploring frequent functional polymorphisms at play in the innate immune response to infection. My discoveries have led to greater insight into the unique attributes that soluble and cellular components of the innate immune system of humans bring to the microbe-host interface, primarily in the context of TB infection.

I have placed great emphasis on education and mentoring throughout my career, particularly in clinical and translational research, and have been committed to building strong interdisciplinary academic programs. I have been/am a faculty member of 10 pre- and post-doctoral training programs (NIH and HHMI) and am PI of 2 NIH T32 training grants. In all, I have mentored ~150 trainees at all levels (15 PhD level scientists, including a DVM PhD graduate of this program), several of whom have been awarded national research fellowships (34 in total) and have gone on to academic or industry positions. I became director of the OSU Medical Scientist Program (MD PhD granting) in 2008 and was awarded the first ever NIH-funded Medical Scientist Training Program (MSTP) in 2011 (renewed in 2016). I am a current member of the AAMC GREAT MD-PhD Section Steering Committee and chair-elect of this group.

B. Positions and Honors

Positions and Employment

1982-1986	Resident and Chief Medical Resident, University of Michigan Hospitals, Ann Arbor, MI
1986-1988	Clinical Fellow, Infectious Diseases, UCLA Medical Center, Los Angeles, CA
1988-1991	Postgraduate Researcher, Bacterial Pathogenesis, UCLA Medical Center, Los Angeles, CA
1991-1996	Assistant Professor, Internal Medicine, University of Iowa, Iowa City, IA
1991-2003	Staff Physician, VA Medical Center, Iowa City, IA
1996-2002	Associate Professor with Tenure, Internal Medicine, University of Iowa, Iowa City, IA

1999-2003	Associate Professor, Department of Microbiology, University of Iowa, Iowa City, IA
2002	Professor, Internal Medicine, University of Iowa, Iowa City, IA
2002-present	Samuel Saslaw Professor of Medicine, The Ohio State University, Columbus, OH
2002-2011	Director, Division of Infectious Diseases, The Ohio State University, Columbus, OH
2002-present	Director, Center for Microbial Interface Biology, The Ohio State University, Columbus, OH
2002-present	Professor, Molecular Virology, Immunology and Medical Genetics, The OSU
2005-present	Professor, Department of Microbiology, The Ohio State University
2005-present	Graduate Faculty, Dept. Veterinary Biosciences, College of Vet Med, The OSU
2008-present	Director, Medical Scientist Training Program, The Ohio State University
2009-present	Professor, Division of EHS, College of Public Health, The Ohio State University
2011-present	Chair, Department of Microbial Infection & Immunity, The Ohio State University

Other Experience and Professional Memberships

1981	AOA, Rutgers Med School
1985	House Officer Research Award, Dept Med, U Mich
1991	Florence Lindsay Trust Award for Research in Biochemistry, COM, U Iowa
1993	ICAAC Young Investigator Award
1997	Fellow, IDSA
1999	Chairman, TB Committee, IDSA
2000	Chairman, Division U, Mycobacteria, ASM
2003	Nelson Distinguished Lecturer, Montana State U
2005	Executive Board, Great Lakes NIH RCE for Biodefense
2006	Unverferth Research Award, Dept Med, Ohio State; Chair, NIH study section panels (Special emphasis panel P01, 2004; ZRG1 IDM, 2004, 2005; ZAI1 DDS-M, 2006)
2007-2011	Member, CRFS NIH Study Section (Chair 10/09-06/11)
2008	Fellow, AAAS
2008	Councilor, CSCR
2011	OSU Distinguished Scholar
2011	Fellow, American Academy of Microbiology
2012	Harrington Innovator Scholar
2013	NIH, NIAID Council Member
2015	College of Medicine Distinguished Professor Award
2016	Association of American Physicians

C. Contributions to Science

1. The primary focus of my research program has been on understanding the **human mononuclear phagocyte response to intracellular pathogens**. As a cellular immunologist, I have been particularly interested in the molecular determinants and pathways involved. My laboratory has made fundamental discoveries regarding the phagocytic receptors for pathogenic mycobacteria and *Francisella*, and continues to address the question of how the interplay of phagocytic receptors and PRRs at the cell surface dictates post-phagocytic events in the cell such as signaling, trafficking, the oxidative response, cell death and cytokine production. The earliest host cell responses are shaped by receptor-mediated signaling events which we have termed “Step 1” (JEM, 2005) which are often overlooked in the microbial pathogenesis field. Selected publications:

    a. Kang PB, Azad AK, Torrelles JB, Kaufman TM, Beharka A, Tibesar E, **Schlesinger LS**. The human macrophage mannose receptor directs *Mycobacterium tuberculosis* lipoarabinomannan-mediated phagosome biogenesis. JEM 202:987-999, 2005. PMCID: PMC2213176.
    b. Rajaram MVS, Morris JD, Brooks MN, Torrelles JB, Azad AK, **Schlesinger LS**. *Mycobacterium tuberculosis* activates human macrophage PPARγ linking mannose receptor recognition to regulation of immune responses. J. Immunol. 185:929-42, 2010 (featured). PMCID: PMC3014549.
    c. Rajaram MVS, Ni B, Morris JD, Brooks MN, Carlson TK, Torrelles JB, **Schlesinger LS**. *M. tuberculosis* lipomannan blocks TNF biosynthesis by regulating macrophage MAP Kinase-Activated Protein Kinase 2 (MK2) and miR125b. PNAS 108:17408-17413, 2011. PMCID: PMC3198317.

2. A second major area of research in my laboratory is regarding increasing our understanding **how the lung alveolar environment "shapes" the biology of AMs in ways that directly impact the host response to airborne infectious agents**. The upper airways clear almost all of the particulates we inhale through multiple mechanisms whereas the deep segments of the lung (terminal airways and alveoli) have evolved for their primary function of gas exchange, an environment where excessive inflammatory responses can be detrimental to health. Thus, inflammatory responses of AMs are tightly regulated. We have made fundamental discoveries regarding the effects of surfactant, in which AMs are bathed, on dampening the immune responses of AMs. We have coined the phrase "switching time" (PNAS, 2009) to reflect a period of relative sluggish response to pathogens before a more robust inflammatory response kicks in, a concept that is advantageous to host-adapted airborne pathogens like *M. tuberculosis*. I have published ~40 papers on this topic. Selected publications:

    a. Ferguson JS, Weis JJ, Martin JL, **Schlesinger LS**. Complement protein C3 binding to *Mycobacterium tuberculosis* is initiated by the classical pathway in human bronchoalveolar lavage fluid. Infect. Immun. 72:2564-2573, 2004. PMCID: PMC387845
    b. Henning LN, Azad AK, Parsa KVL, Crowther JE, Tridandapani S, **Schlesinger LS**. Pulmonary Surfactant Protein-A: A key regulator of Toll-Like Receptor expression and activity in human macrophages. J. Immunol. 180:7847-7858, 2008. PMCID: PMC2562757.
    c. Day J, Friedman A, **Schlesinger LS**. Modeling the immune rheostat of macrophages in the lung in response to infection. PNAS. 106:11246-11251, 2009. PMCID: PMC2708732.
    d. Nguyen HA, Rajaram MVS, Meyer D, **Schlesinger LS**. Pulmonary surfactant protein-A and surfactant lipids up-regulate IRAK-M, a negative regulator of TLR-mediated inflammation in human macrophages. Am J Physiol Lung Cell Mol Physiol. 303:L608-16, 2012. PMCID: PMC3469587

3. Newer areas of my research program pertain to the **impact of diabetes on the mononuclear phagocyte response to *M. tuberculosis*, host susceptibility in the innate immune system to infection, and new imaging and drug discovery platforms for mycobacteria**, where I lead a group of investigators in my Center. I am a Harrington Drug Discovery Institute Scholar and have acquired funding through the NIH and other private partnerships. I have published ~14 papers on these subjects. Selected publications:

    a. Salunke SB, Azad AK, Kapuriya NP, Balada-Llasat J-M, Pancholi P, **Schlesinger LS**, Chen CS. Design and synthesis of novel anti-tuberculosis agents from the celecoxib pharmacophore. Bioorganic & Medicinal Chemistry. In press
    b. Azad AK, Curtis A, Papp A, Webb A, Knoell D, Sadee W, **Schlesinger LS**. Allelic mRNA expression imbalance in C-type lectins reveals a frequent regulatory SNP in the human surfactant protein A (SP-A) gene. Genes and Immunity 14:99-106, 2013. PMCID: PMC3594410.
    c. Restrepo BI, Twahirwa M, **Schlesinger LS**. Phagocytosis via complement or Fc-gamma receptors is compromised in monocytes from type 2 diabetes patients with chronic hyperglycemia. PLoS ONE 9:e92977, 2014. PMCID: PMC3966862.
    d. Guirado E, Mbawuike U, Keiser TL, Arcos J, Azad AK, Wang S-H, **Schlesinger LS**. Characterization of host and microbial determinants in individuals with latent tuberculosis infection using a human granuloma model. mBio. 6:e02537-14, 2015. PMCID: PMC4337582

4. My research also focuses on the **pathogenesis and immune response to *Francisella tularensis* infection in human mononuclear phagocytes**. This topic is directly related to the current proposal. We have determined that pathogenic *Francisella* activate complement, but are resistant to complement-mediated lysis in part due to limited C3 deposition and the presence of LPS O Ag. We have shown that highly virulent *F. tularensis* uses macrophage CR3 for efficient uptake which leads to down-regulation of TLR2-dependent pro-inflammatory responses by inhibiting MAPK activation through outside-in signaling. CR3-linked immune suppression is an important mechanism involved in the pathogenesis of *F. tularensis* infection. Based on these findings we have published a mathematical model that explains the possible mechanism of how CR3 can inhibit ERK activity through synergy of Akt kinas and Ras-GAP. Select pubs.

    a. Clay CD, Soni S, Gunn JS, **Schlesinger LS**. Evasion of complement-mediated lysis and complement C3 deposition are regulated by *Francisella tularensis* lipopolysaccharide O antigen. J. Immunol. 8:5568-78, 2008. PMCID: PMC2782685.
    b. Shipan Dai, **Rajaram MVS**, Heather M. Curry, Rachel Leander and Larry S. Schlesinger. (2013). Fine tuning inflammation at the front door: Macrophage Complement Receptor 3 mediated phagocytosis and immune suppression for *Francisella tularensis.* PLoS Pathogens. 9:e1003114, 2013. PMID:23359218.

c. Leander R, Dai S, **Schlesinger LS** and Friedman, A. A mathematical model of CR3/TLR2 crosstalk in the context of Francisella tularensis infection. PLoS Comput Biol. 8: e1002757, 2012. PMCID: PM3486853

5. I have been committed to research in **aging and tuberculosis** for the past 4 years. I have become particularly interested in the unique signature of the baseline inflammatory monocyte/macrophage in the setting of aging. This type of baseline inflammation is also seen in other disease states, making this research broadly applicable and important to pursue.

   a. Canan CW, Gokhale N, Carruthers B, Lafuse WP, **Schlesinger LS**, Torrelles JB, Turner T. Characterization of Lung Inflammation and its Impact on Macrophage Function in Aging. J. Leuk. Biol. 96:473, 2014. PMCID: PMC4632167
   b. Moliva JI, Rajaram MVS, Sidiki S, Sasindran SJ, Guirado E, Pan X, Wang SH, Ross P Jr., Lafuse WP, **Schlesinger LS**, Turner J*, JB Torrelles JB*. 2014. Molecular Composition of the Alveolar Lining Fluid in the Aging Lung. AGE. 36:1187, 2014. * Co-corresponding authors. PMCID: PMC4082594.

URL to a full list of published work:
http://www.ncbi.nlm.nih.gov/sites/myncbi/larry.schlesinger.1/bibliography/40327053/public/?sort=date&direction=ascending

D. Research Support
Active

R01 AI059639 Schlesinger (PI) 08/01/12-07/31/17
TB and innate immune regulation of lung macrophages
This grant explores the role of surfactant in the *M.tb*-mononuclear phagocyte interaction

R01 AI116039 Ronacher (PI) 02/10/15-01/31/20
Altered immune-endocrine axis in type 2 diabetes and tuberculosis risk
This grant explores the impact of diabetes on the immune response to *M.tb*
Role: Co-Investigator

R21/R33 AI102252 Ainslie (PI) 07/01/12-06/30/17
Celecoxib Derivative: Host Cell-Directed Inhibitors of Intracellular Pathogens
This grant explores a new set of compounds for activity against *M.tb*
Role: Co-Investigator

R01 HL127651 Amer (PI) 07/20/15-06/30/19
The role of microRNA-calibrated autophagy in innate immunity and inflammation
This grant explores the epigenetic changes and other mechanisms leading to increased expression of miRs in CF patients and mice and their therapeutic modification
Role: Co-investigator

P01 AG051428 Turner (PI) 03/15/16-02/28/21
Exploring the impact of inflammaging on immune function during M.tb infection
This grant assesses alterations in inflammation during aging that impact tuberculosis
Role: Project 1 Co-investigator, Project 2 PI

R01 AI123253 Zhang (PI) 04/01/16-03/31/21
Regulation of innate immune system sensing of C. albicans infection
This grant explores regulation of C-type lectins in response to fungi
Role: Co-investigator

T32 AI112542 Schlesinger (MPI) 08/15/14-07/31/19
Interdisciplinary Program in Microbe-Host Biology
This is a pre- and post-doctoral training grant in microbial pathogenesis

T32 GM075787 Schlesinger (PI) 07/01/11-06/30/16
Medical Scientist Training Program - Ohio State University
This is a pre-doctoral training grant of MD PhD students

Bill and Melinda Gates Foundation Schlesinger (PI) 07/01/15-06/30/17

Alveolar macrophage immunobiology and functional genomics: Unlocking human to human variation in host response to *M. tuberculosis*.
This grant explores the human to human variation in macrophage immune responses to *M.tb*

ARNO Industry Contract Schlesinger (PI) 04/01/13-09/30/16
ARNO Therapeutics
Center for Microbial Interface Biology infectious diseases AR-12 drug discovery program collaboration with ARNO Therapeutics
The goal of this grant is to explore the anti-infective activity of AR-12 against multiple pathogens

Completed Research Support (completed during the last three years)
Navidea Biopharmaceuticals Industry Schlesinger (PI) 01/01/13-12/01/16
Navidea
Tilmanocept for diagnosis and therapy of inflammatory diseases
This grant explores the use of Tilmanocept and derived compounds for targeted diagnostics and therapies for human diseases

Harrington-Scholar Innovator Grant Schlesinger (PI) 01/01/13-12/31/15
University Hospitals of Cleveland
Anti-TB drug discovery through lead optimization of the protein kinase inhibitor OSU-03012
The goal is to identify a new class of compounds with activity against *M. tuberculosis*

U54AI057153 Schneewind (PI) 03/01/09-02/01/15
Great Lakes RCE for Biodefense and Emerging Infectious Disease Research
Host and bacterial targets mediating immune suppression in pneumonic tularemia
This grant explores the lung innate immune responses to *Francisella tularensis*, the causative bacterium of tularemia.
Role: PI research project

College of Medicine Bridge Funding Grant Program Turner (PI) 07/01/14-06/30/15
Exploring the impact of inflammaging on immune function during M.tb infection
The goal of this bridge is to support the generation of preliminary data for a P01 submission.
Role: Co-Investigator

OSU PHPID Strategic Area Grant Schlesinger (PI) 10/01/12-10/09/14
Anti-tuberculosis drug discovery through lead optimization of the protein kinase inhibitor OSU-03012
The goal is to identify a new class of compounds with activity against *M. tuberculosis*

Public Health Preparedness for Infectious Diseases Turner (PI) 10/01/12-09/31/14
Exploring the impact of inflammaging on immune function during M.tb infection
The goal of this OSU interdisciplinary grant is to support the generation of preliminary data for a P01.
Role: Co-Investigator

R01 HL094586 Amer (PI) 08/01/09-05/01/14
Role of caspases in Legionella pneumophila pulmonary infection
The goal of this grant is to study the role of caspases and NOD proteins in controlling the intracellular fate of Legionella pneumophila in macrophages.
Role: Co-PI

R01 AI059639 Schlesinger (PI) 08/01/12-07/01/13
Diversity supplement: TB and innate immune regulation of lung macrophages
This is a diversity supplement to support Ms. Uchenna Mbawuike's research in the laboratory