WELDON SCHOOL OF BIOMEDICAL ENGINEERING

PURDUE UNIVERSITY

BME SPECIAL RESEARCH SEMINAR
Wednesday, March 27, 2024
2:00 – 3:00 pm, MJIS 2001
ZOOM LINK https://purdue-edu.zoom.us/j/98508885744

"The *M. tuberculosis*-macrophage encounter: From basic science discovery to a potential host-directed therapy for tuberculosis"

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Abstract: The Schlesinger lab explores human mononuclear phagocyte biology and the pathogenesis of tuberculosis (TB) and diseases due to other airborne intracellular pathogens that subvert lung immune mechanisms. These studies include the impact of HIV, aging and diabetes on cellular function in TB. We develop human in vitro models as a bridge to therapies, focusing on druggable pathways for host-directed therapies (HDT) for infectious diseases. Backed by fundamental findings in the lab, our recent studies provide evidence that inducing intrinsic/mitochondrial based apoptosis limits intracellular *M.tb* growth. We used specific inhibitors of MCL-1 and BCL-2, which are key regulatory proteins that normally inhibit apoptosis and so have been heavily targeted for cancer treatment. We considered repurposing cancer chemotherapies and thereby used an FDA-approved BCL-2 inhibitor that was awarded breakthrough designation by the FDA in 2017, in combination with MCL-1 inhibitors that are in phase I/II clinical trials for cancer therapy. For the first time, we show that specifically combining MCL-1 and BCL-2 inhibitors to induce apoptosis of *M.tb*-infected macrophages: 1) limits *M.tb* growth in both human and murine macrophages, 2) reduces growth of drug resistant *M.tb* to a similar extent as drug susceptible *M.tb*, 3) combines with antibiotic treatment to more effectively reduce *M.tb* growth than antibiotics or MCL-1 and BCL-2 inhibitors alone and 4) reduces *M.tb* burden in a pre-clinical human granuloma model. This work uncovers targeting the intrinsic apoptosis pathway as a promising approach for drug-susceptible and -resistant TB HDT. As apoptosis is associated with improved antigen presentation and reduced inflammation, it could boost the immune response while limiting damaging tissue inflammation associated with TB disease. Since safety and activity studies are underway in cancer clinics for MCL-1 and BCL-2 inhibitors, re-purposing them for TB treatment should translate more readily and rapidly to the clinic.

***Biography*:** Dr. Schlesinger is a leading physician scientist focused on how the lung environment shapes alveolar macrophage biology in the context of the pathogenesis of tuberculosis and lung diseases caused by other intracellular pathogens that subvert lung immunity. He translates these discoveries into new human-based platforms and assays for host-directed therapies for infectious diseases. He is a prolific scholar, having authored 240 peer-reviewed articles and reviews, served as editor of 2 books and has written several chapters in leading textbooks. He has been continually funded by the NIH and other federal agencies as well as private foundations such as the Bill & Melinda Gates Foundation for more than 30 years. He has trained ~ 175 individuals and led NIH-funded training programs. He is a past NIH NIAID Council member, Fellow of the American Association for the Advancement of Science, Infectious Diseases Society of America, Association of American Physicians and American Academy of Microbiology. Dr. Schlesinger received his BA from Cornell University, MD from Rutgers University, and clinical and research Fellowships at UCLA Health. He has held faculty appointments at the University of Iowa and The Ohio State University, the latter as director the Division of Infectious Diseases, founding chair of the Department of Microbial Infection & Immunity and director of the Infectious Diseases Institute.