THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

MARIAM IBRAHIM

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE

GRADUATE COLLEGE
DEPARTMENT OF
GRADUATE PHARMACEUTICAL SCIENCES

Wednesday, February 15, 2017, 2:00 p.m.
Room 103, College of Pharmacy, OUHSC

FORMULATION, CHARACTERIZATION AND EVALUATION OF ADVANCED PULMONARY DELIVERY SYSTEMS FOR ANTI-TUBERCULOSIS DRUGS

COMMITTEE IN CHARGE: Lucila Garcia-Contreras, Ph.D., Chair, Doris M. Benbrook, Ph.D., David L. Johnson, Ph.D., Michael A. Ihnat, Ph.D., William M. McShan, Ph.D.

ABSTRACT: Tuberculosis (TB) is a life threatening infection caused by *Mycobacterium tuberculosis* (MTB). The severe side effects associated with current TB treatments often decrease patient compliance and increase the probability of the emergence of multidrug resistant MTB strains. Therefore, new drugs with fewer side effects and different mechanism of action to that of the existing drugs are needed to address the global TB epidemic. SHetA2, an anticancer drug, is active against MTB, but its poor aqueous solubility yields low oral bioavailability. Pulmonary administration of SHetA2 for TB treatment would overcome these limitations and would deliver SHetA2 directly to the lungs, the main site of TB infection. We hypothesized that pulmonary delivery of SHetA2 as dry powder aerosol can achieve local therapeutic drug concentrations that would significantly reduce the extent of infection. Using the quality by design approach, we designed, optimized and

manufactured three different formulations of SHetA2 microparticles (MPs), SHetA2 alone, SHetA2 PLGA and SHetA2 mannitol MPs, to maximize the drug dose, target alveolar macrophages and increase drug solubility, respectively. The three SHetA2 MPs had optimum properties for alveolar deposition and were chemically stable. Manufacture by spray drying physically transformed the crystalline structure of SHetA2 to the amorphous form, which significantly increased its solubility. All SHetA2 MPs were efficiently dispersed with the Aerolizer® dry powder inhaler, as indicated by the high respirable fraction after aerosolization into a next generation impactor. Moreover, the respirable fraction of SHetA2 MPs dissolved much faster and to a greater extent than the unprocessed drug. All SHetA2 MP formulations were highly uptaken by macrophages and *in vitro* efficacy studies demonstrated the efficacy of SHetA2 MPs in killing intracellular MTB. Our mechanistic studies designed to gain insight into the mechanism by which SHetA2 kills MTB identified MTB DnaK as a protein target for SHetA2 in MTB. Our preliminary results suggest that the interference of SHetA2 in the binding of MTB DnaK and Y1636 stress proteins could be such mechanism, in a manner similar to the way SHetA2 disrupts mortalin/p53 binding for its anticancer activity.