THE GRADUATE COLLEGE OF THE

UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

ANKUR SHARMA

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE

DEPARTMENT OF GRADUATE PHARMACEUTICAL SCIENCES

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Room 339, College of Pharmacy, OUHSC

PHARMACOKINETIC AND PHARMACODYNAMIC CHARACTERIZATION OF SHETA2, A NOVEL ORALLY BIOAVAILABLE ANTI-CANCER DRUG TOWARDS CLINICAL TRANSLATION

COMMITTEE IN CHARGE: Sukyung Woo, Ph.D., Chair, Doris M. Benbrook, Ph.D., Nathan Shankar, Ph.D., Michael A. Ihnat, Ph.D., Wei Yue, Ph.D.

ABSTRACT: SHetA2 is a flexible heteroarotinoid (Flex-Het), which was selected as a lead from a series of Flex-Het based on potent induction of apoptosis in cancer cells. With the promising preclinical safety and efficacy profiles, SHetA2 is now moved forward for clinical development. Well-designed experiments in preclinical animal models and utilization of physiologically, mechanism-based pharmacokinetic and pharmacodynamic (PBPK/PD) models can provide better quantitation and prediction of the disposition and dynamics of SHetA2. The main goal of this thesis was to develop PBPK/PD models for SHetA2 that not only can provide improved understanding of SHetA2 PK/PD but also can assist more

rationale design of Phase 0/I clinical trials of SHetA2, thereby decreasing risk of failure at the clinical development stage and making the clinical trial cost effective.

Chapter 2 focuses on characterization of preclinical PK and allometric scaling to predict human PK profile and the first-in-human dose. SHetA2 exhibited complex absorption kinetics and dose-limited bioavailability due to the absorption saturation, which has taken into consideration for the first-in-human dose. In Chapter 3, a simple, cost-effective, and sensitive HPLC-UV method was developed and validated for the determination of SHetA2 in various biological samples. Chapter 4 involves characterization of SHetA2 tissue distribution in tumor bearing mice by developing a whole body PBPK model. This PBPK model can be scaled-up to predict the drug exposure at tumor sites or local sites of action in humans. Chapter 5 studied the dynamics of drug-induced apoptosis by measuring caspase-cleaved cytokeratin-18 (CK-18) released from the apoptotic carcinoma cells into the blood, and drug induced G1 cell cycle arrest by measuring tumor cyclin D1 protein as potential PD biomarkers. The developed PBPK model was expanded and linked with the drug-induced effects to establish dose-exposure-biomarkers-efficacy relationship.

This thesis reflects our endeavors to integrate PK and PD characteristics of SHetA2 learned over the years from various preclinical studies via development of comprehensive PBPK/PD model. Our studies demonstrated how utilization of various PK/PD tools and principles could assist selection of rationale dosage regimens and study designs, thereby making the clinical trials safe, cost effective and decreasing failure rate of early drug development.