THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Pharavee Jaiprasart

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE
Department of Pharmaceutical Sciences

December 8, 2017 | Time 12:00 pm
College of Pharmacy Building, Room 101

Quantitative Systems Pharmacology Approach for a Rational Development of Gene-Targeting Combination Cancer Therapy

COMMITTEE IN CHARGE: Sukyung Woo, PhD, Chair
Jessie L.-S. Au, PharmD, PhD; Kelly Standifer, PhD
Youngjae You, PhD; Takemi Tanaka, PhD

ABSTRACT:

Combination therapy is an important treatment modality for various diseases including cancer. Because the number of possible combinations can be prohibitively large, utilization of Quantitative Systems Pharmacology (QSP) models can enhance the understanding of interactions and can help to select the best combinations for further development. The objectives of this thesis are to provide a framework for a rationale development of combination gene-targeting therapy by utilizing QSP models to predict the effects of combination therapy from diverse dosing regimen on target modulation, that not only provide an insight into complex pharmacokinetic and pharmacodynamic interactions of gene targeting agents on multiple levels, but can be used to assist selection of optimal combination regimen for further investigation.

The current study examined (1) the mediators of resistance to antiangiogenic drugs, (2) the mediators of resistance to chemotherapeutics, (3) quantitative contribution and mechanisms in which serum proteins and polyanions impede siRNA therapeutic, and (4) development of predictive QSP models of combination effects utilizing data regarding mechanism of action of the drug and nature of drug-drug interactions which occurs at multiple levels to identify optimal combination regimen of siRNA therapeutic and a cytotoxic agent, suramin.

We identified Apelin/Apelin receptor as a novel mediator of resistance to antiangiogenic drug in preclinical xenograft models. The pathway function in both paracrine and autocrine manner to promote angiogenesis and also directly stimulate cancer cell proliferation and reduced response to vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor. Additionally, because cancer is a complex disease that involves multiple biological interactions, we hypothesized that multiple genes are synergistically involved in treatment resistance to chemotherapy in such a way that inhibition of a single driver gene cannot completely restore tumor sensitivity to the treatment. The present work has shown two lines of investigations to seek support for this hypothesis; retrospective analysis of Big Data (i.e., genomics) from 10 The Cancer Genome Atlas (TCGA) clinical studies and *in silico* simulation. We further described the use of predictive QSP model to identify synergistic combination regimen targeting survivin gene, one of the most well-studied biomarkers and mediators of chemoresistance. We have shown that sequential combination of siRNA targeting survivin gene and suramin resulted in a synergistic and a more complete depletion of survivin mRNA in colorectal cancer cells with aberrant survivin regulation. The developed models quantitatively described the simultaneous combination effect of suramin and lipoplex well. They were also successfully applied to different sequential combination regimens, demonstrating robustness and great utility of our model to assist drug development processes.

This thesis reflects our endeavors to utilize comprehensive QSP models in various steps of drug discovery, from target selection to drug and dose selection. The QSP approach enhances our understanding of interactions and combination effects, which can assist selection of the best combinations for further development. Our success underscores the possibilities of accurate prediction of combination therapy outcome given sufficient understanding of the mechanism of drug interactions.