PhD DEFENCE – Monday, July 27th, 2015

Student: **Kevin Yang**

Title: **DEVELOPMENT OF NOVEL SMALL MOLECULE INHIBITOR OF ANDROGEN RECEPTOR TO TREAT CASTRATION-RESISTANT PROSTATE CANCER**

Time and Location: 08:00 am, Dorothy Lam Board Room, BC Cancer Research Centre

Supervisor: Dr. Marianne Sadar

ABSTRACT

Androgen receptor (AR), a transcription factor, is a validated therapeutic target for prostate cancer. All current AR-targeting therapies inhibit the growth of prostate cancer cells by blocking the ligand-binding domain (LBD), where androgen binds to activate the receptor. Unfortunately, these therapies fail to maintain a durable clinical effectiveness, as patients eventually succumb to metastatic castrationresistant prostate cancer (CRPC). The clinical onset and progression of most CRPC is accompanied by rising levels of serum PSA, which is a gene transcriptionally regulated by AR. This indicates aberrant AR transcriptional activity is involved in driving CRPC and conferring therapy-resistance. Therefore, it is imperative to continue the research and development of novel AR inhibitors that can overcomemolecular mechanisms underlying aberrant AR transcriptional activity. This dissertation presents three research projects: 1) Discovery of novel AR inhibitors; 2) Evaluation of EPI-002, an AR N-terminal domain (NTD) antagonist, for inhibiting aberrant AR transcriptional activity; and 3) Generation of a prostate cancer model resistant to EPI-002.

To discover novel AR inhibitors, candidate compounds identified from high throughput screening were characterized by fluorescent ligand binding assays, ARdriven reporter assays, qPCR gene expression analyses, and BrdU-labeling proliferation assays. AR NTD inhibitor EPI-002 was evaluated against several mechanisms believed to cause aberrant AR transcriptional activity, including coactivator overexpression, AR LBD gain-of-function mutations, and constitutively active AR splice variants with truncated LBD. To generate a prostate cancer model resistant to EPI-002, LNCaP human prostate cancer cells were cultured under chronic EPI-002 exposure.

First, spongian diterpenoids was discovered as novel antiandrogens that bind to the AR LBD. The diterpenoids blocked androgen-dependent AR transcriptional activity with structure-activity relationship, reduced androgen-regulated gene expression, and inhibited androgen-sensitive prostate cancer cell proliferation. Secondly, EPI-002 was effective against aberrant AR transcriptional activities caused by overexpressed coactivators, AR LBD gain-of-function mutations, and constitutively active AR splice variant AR-V7. Importantly, EPI-002 inhibited the growth of CRPC cells driven by AR-V7, whereas antiandrogen had no effect. Finally, a human prostate

cancer cell line model resistant to growth inhibition by EPI-002 was generated, allowing future studies to investigate mechanisms of resistance against AR inhibition through the NTD.