

University of Maryland Baltimore Graduate School

Announcement of Doctoral Dissertation Defense*

Candidate: Adam Schayowitz

Date, Time, and Place: January 24, 9am, HFSII Auditorium

Dissertation Title: The Synergistic Effect of Anti-androgens and Signal Transduction Inhibitors in Prostate Cancer Progression

Dissertation Abstract**:

Androgen ablation is the standard treatment for advanced disease. Despite initial success, approximately 70% of patients eventually progress to hormone refractory prostate cancer (HRPC). To investigate the mechanisms of this resistance we utilized human prostate cancer cells (LNCaP) to create a hormone refractory prostate cancer (HRPC) model which mimics disease progression (HP-LNCaP). Our novel anti-androgen/androgen synthesis inhibitor, VN/124-1, proved to be a potent inhibitor of proliferation and AR activation in hormone dependent and hormone refractory prostate cancer cell lines (HP-LNCaP). Anti-androgen treatment also resulted in increased expression of multiple signal transduction pathways (STPs). However, compared to hormone sensitive cells, resistant cells demonstrated a higher level of STPs. Inhibition of STPs such as mTOR and EGFR in resistant cells resulted in decreased protein expression and increased AR expression and activation. These findings demonstrated that a compensatory signaling mechanism and cross-talk between AR and PI3K/Akt/mTOR pathways occurs with androgen ablation in vitro. As such, we investigated the effect of dual inhibition and found that combination treatment with VN/124-1 and everolimus (mTOR inhibitor) or gefitinib (EGFR/HER-2 inhibitor), caused significant inhibition of cell proliferation in our HRPC model. We further analyzed the interaction of the AR and mTOR pathways. Using co-immunoprecipitation of Akt and AR, it was found that the interaction between the pathways increases 7-fold as cells progressed from a hormone sensitive to hormone resistant model. The interaction was reduced dramatically with VN/124-1 plus everolimus. Our in vitro findings were supported by xenograft investigations. The addition of everolimus to bicalutamide treatment of resistant tumors significantly decreased growth rate and tumor volume compared to single agent bicalutamide ($p=0.0001$) or everolimus ($p=0.04$). Analysis of tumors demonstrated that anti-androgen treatment increased IGFR, p-Akt, p-70S6K and p-P6S6 protein expression compared to control xenografts. In summary, as tumors progress on anti-androgen therapy, there is an increase in signal transduction pathway activation compared to controls. As such, the combination of anti-androgen, VN/124-1, and mTOR inhibitors from the beginning significantly reduced tumor volume compared to everolimus or bicalutamide alone in HRPC xenografts.