RET Kinase as a Driver of Neuroendocrine Prostate Cancer

Halena VanDeusen[a], Johnny Ramroop[b], Katherine Morel[c], SongYi Bae[a], Justin Hwang[d], Ashley Petersen[e], Zoi Sychev[a], Colm Morrissey[f], Peter S. Nelson[g], Leigh Ellis[c], **Justin M. Drake[a]**

Department of Pharmacology[a] or Biostatistics[e], University of Minnesota; Medicine[b], Rutgers Cancer Institute of New Jersey; Pathology[c] or Medical Oncology[d], Dana-Farber Cancer Institute; Urology[f] or Medical Oncology[g], University of Washington

Background: The implementation of newer second generation hormonal therapies has created a shift in the molecular characteristics of castration resistant prostate cancer (CRPC) tumors, with a greater incidence of tumors that have lost androgen receptor (AR) signaling (collectively termed aggressive variant prostate cancers or AVPC). AVPC most commonly evolves from pre-existing prostate adenocarcinoma (AdCa), may be present in up to 35% of patients with CRPC, and treatment provides modest 1-2 year survival rates due to rapid therapy resistance and disease progression. AVPC tumors may also gain neuroendocrine markers creating a distinct subclass of AVPC known as neuroendocrine prostate cancer (NEPC). However, the mechanisms that drive NEPC is still unclear.

Methods: To understand how these AR negative AVPCs differ from their AR positive counterparts, we analyzed and compared the phosphoproteome of AdCa and AVPC cell lines to identify altered kinase activity between the two groups using kinase substrate enrichment analysis. We utilized mRNA transcript data from multiple patient studies with AVPC and analyzed large publicly available cell line datasets to assess kinase dependency in AVPC vs AdCa cell lines. We then used *in vivo* xenograft and *in vitro* organoid models of AVPC to pharmacologically inhibit RET kinase alone or in combination with enzalutamide.

Results: Our results revealed distinct phosphorylation patterns between AdCa and AVPC and predicted RET activity to be elevated in the AVPC cell lines. Large primary tumor transcript data sets revealed that NEPC patients had higher levels of RET mRNA when compared to AdCa patients. Analysis of publicly available datasets of RET dependency screening and small-cell neuroendocrine (SCN) phenotype evaluation in cancer cell lines revealed that cell lines with higher SCN-like characteristics are more dependent on RET for cell proliferation. In addition, RET dependency exhibited a negative correlation with AR dependency, while a strong correlation with a NEPC driving gene, BRN2. We found that the RET pathway inhibitor, AD80, dramatically increased cell death in cultured mouse organoids and reduced xenograft tumor growth. Treatment with both enzalutamide and AD80 further increased cell death beyond AD80 treatment alone in an AVPC organoid tumor model.

Conclusions: These results implicate RET as an important kinase for NEPC tumor survival and progression and suggests that targeting RET kinase may be a treatment option in patients with AVPC containing NE features.

No conflict of Interest.

Acknowledgements:
PCF Young Investigator Award, DoD PCRP Award