Targeting Androgen Receptor and ACK1 signaling with Novel Epigenetic Therapeutics in Enzalutamide-resistant Castration-Resistant Prostate Cancer

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Background: Over the years it has emerged that tyrosine kinase and androgen receptor (AR) signaling play important roles in the progression of prostate cancer (PC) from a hormone-sensitive to a castration-resistant state. We previously uncovered a novel signaling pathway wherein AR recruits a non-receptor tyrosine kinase, ACK1, to regulate a distinct transcription program leading to AR upregulation. Enzalutamide, a second generation of AR antagonist, and abiraterone, an androgen synthesis inhibitor confer a modest survival advantage for PC patients, often due to upregulation of an AR splice variant, AR-V7. We have generated a new class of inhibitors that target ACK1. Our lead compound, (*R*)-9bMS, not only suppresses ACK1 activity and mitigates AR and AR-V7 expression, but also overcomes enzalutamide resistance.
Methods: In order to conduct the studies necessary to credential (*R*)-9bMS as a treatment approach for PC, we first performed large-scale synthesis of (*R*)-9bMS. We also synthesized various derivatives of (*R*)-9bMS and assessed their kinase specificity and microsomal stability (MSTAB) mouse, rat and human microsomes. In addition, we performed dose-response experiments with (*R*)-9bMS to determine the half maximal inhibitor concentration (IC_{50}) in cell line models of hormone-sensitive, castrate-resistant, enzalutamide-resistant as well as taxane-resistant PC cells.
Results: (*R*)-9bMS was observed to be highly stable in human and rat microsomes. Further, (*R*)-9bMS inhibited growth of castrate-resistant, enzalutamide-resistant and taxane-resistant PC cells and also suppressed cell migration. Moreover, (*R*)-9bMS was found to be highly effective in suppressing prostate tumor growth in mice bearing human prostate cancer cell xenografts when (*R*)-9bMS was given orally at 130 mg/kg/day.
Conclusion: These data suggest that (*R*)-9bMS is effective at inhibiting proliferation and migration in multiple models of PC, including castrate-resistant and enzalutamide-resistant, and that oral administration of (*R*)-9bMS is effective at suppressing growth in mouse models of PC. Our data suggest that inhibiting ACK1 using an oral formulation of drug may be a realistic option in future clinical trials.

Conflict of Interest: The Moffitt Cancer Center has filed patent applications as follows: "Antibodies specific for phosphorylated histones and uses thereof" (US patent no. 9,594,084) and "Inhibitors of ACK1/TNK2 Tyrosine Kinase" (US patent no 9,850,216). N.M. is named as inventors on these patents and both the patents have been licensed by TechnoGenesys, Inc. N.M. is a co-founder of TechnoGenesys, Inc., own stock, and serve as consultants for TechnoGenesys, Inc.

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