A novel therapeutic agent (\(R\))-9bMS for treatment of Castration Resistant Prostate Cancer

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**Background:** Earlier we have uncovered that ACK1 tyrosine kinase not only interact with androgen receptor (AR), but also regulates its expression by phosphorylating histones in AR enhancer, thereby activating transcription even in presence of Enzalutamide, a second generation of AR antagonist, and abiraterone, an androgen synthesis inhibitor. These data prompted us to take up development of ACK1 inhibitor; our lead compound, (\(R\))-9bMS, not only suppressed ACK1 activity and mitigates AR and AR-V7 expression, but also overcame 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 GLP-grade 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 PC cells. Further, we performed GLP-Tox studies in rats.

**Results:** (\(R\))-9bMS was observed to be highly stable in human and rat microsomes. Further, (\(R\))-9bMS inhibited growth of castrate-resistant, enzalutamide-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 and subcutaneously. (\(R\))-9bMS appears to be well tolerated; 5 weeks/5 days per week at 130 mg/kg in the CRPC model exhibited no toxicity in mice. Also, maximum tolerated dose (MTD) in a 10 day rat study showed the drug to be not toxic to up to 60 mg/kg.

**Conclusion:** These data suggest that (\(R\))-9bMS is effective at inhibiting proliferation and migration of CRPCs in multiple mouse models of PC, including castrate-resistant and enzalutamide-resistant. Further, these data indicates that oral as well as subcutaneous administration of (\(R\))-9bMS is effective at suppressing growth in mouse models of PC. In addition, GLP-Tox studies indicates that (\(R\))-9bMS is not toxic up to 130 mg/Kg dose in mice. Overall, our data suggest that inhibiting ACK1 using an oral formulation of drug may be a realistic option in future clinical trials.

**Conflict of Interest:** (\(R\))-9bMS compound has been patented- “Inhibitors of ACK1/TNK2 Tyrosine Kinase” (US patent nos. 9,850,216 and 10,850,216 ). 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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