Development of Novel, Selective, Orally Available Small Molecule CDK9 Inhibitors for Prostate Cancer Therapy - Mechanistic Studies

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Development of Novel, Selective, Orally Available Small Molecule CDK9 Inhibitors for Prostate Cancer Therapy - Mechanistic studies Abstract: Amplification of N-MYC causes its overexpression in Neuroendocrine Prostate Cancer (NEPC) patients, and it is a rare lethal subtype of cancer detected in 2% of all Prostate Cancers (PC) and over 10-17% of mCRPC (Metastatic Castration-Resistant PC) patients. N-MYC and activated CDK9 function as oncogenic drivers sufficient to transform human-derived prostate cancer cells to take on NEPC phenotypic changes resulting in a more aggressive disease identified in late-stage human PC patients. Additionally, N-MYC is associated with tumor resistance, and its downregulation through CDK9 inhibitors lessens tumor burden. Our efforts in this study proved that the targeting of N-NYC as a driver of NEPC with CDK9 inhibitors such as OLX-3030 and its series could be a viable approach for therapeutic intervention of mCRPC and NEPCs. We performed the western blot experiments utilizing the novel small molecule CDK9 inhibitor OLX-3030, its analogues, and reference compound AZD-4573 against prostate cancer cells; DU145 including NEPC cell lines; 22RV1 and LASCPC01. Our lead CDK9 inhibitor OLX-3030 exhibited potent activity in inhibiting DU-145, 22RV1, and LASCPC-01 cell lines. These results were comparable to that of the reference compound AZD-4574 which is a clinical-stage agent in development by AstraZeneca. In summary, OLX-3030 and its analogues displayed promising activities in both androgen receptor-positive, and NEPC cells by down-regulating N-MYC, C-MYC, and super-enhancer genes such as MCL-1. We conclude that OLX-3030 had the appropriate qualities for development as a pre-clinical candidate.

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