Novel small molecule inhibitors of p300/CBP down-regulate AR and c-Myc for the treatment of castrate resistant prostate cancer

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Introduction

- Targeted degradation of androgen receptor (AR) and androgen receptor variants (ARV) represents an important therapeutic opportunity for patients with castration resistant prostate cancer.
- EIA binding protein (p300) and CREB binding protein (CBP) are two closely related histone acetyltransferase enzymes that act as transcriptional co-activators of AR.
- We have developed potent, selective and orally active small molecule inhibitors of the bromodomain of p300/CBP and report here, their impact on AR, ARv and ARv expression and function.
- We have also examined their role in driving synthetic lethality. Loss of function mutations in either p300 or CBP (present in significant proportions of lung and bladder tumours) can lead to dependancy on the corresponding paralogous protein.

1. CCS series selectivity

3. CCS357 degrades AR-FL & AR-SV protein & reduces expression of AR-target genes in 22Rv1 cells

4. CCS357 degrades AR & AR-SV protein; JQ1 (BRD4 inhibitor) has no effect

5. Combination benefit of p300/CBP inhibitors with a CD46/4 or PARP inhibitor

6. AR, AR-SV and cMyc protein levels are reduced following single oral dose in 22Rv1 xenograft.

7. In vivo efficacy in 22Rv1 xenograft: Including continued tumour growth block following drug withdrawal

8. Protein biomarkers are reduced in 22Rv1 tumour bearing animals treated with CCS4177 for 7 and 28 days

9. Plasma PSA is reduced in 22Rv1 tumour bearing animals treated with CCS1477

10. Effects of p300/CBP and BET inhibition on cell proliferation in wild-type and CBP deficient cell lines in vitro; also distinct from BET inhibition (JQ1)

Conclusions

- Small molecule inhibition of the bromodomain of p300/CBP, leads to down-regulation of AR, AR-SV and c-Myc, as well as inhibiting key downstream genes, including PSA and TMPRSS2.
- CCS4177, a clinical candidate, causes complete tumour growth inhibition in a 22Rv1 xenograft model at doses which are well tolerated. Inhibition is seen of tumour AR, AR-SV, as well as plasma PSA. The tumour growth inhibition caused by CCS4177 is sustained following drug withdrawal.
- AR, AR-SV and c-Myc are reduced following a single 30mg/kg dose of CCS4177. Cleaved PARP is increased at a higher dose of 100mg/kg.
- Combination benefit is observed after inhibition of p300/CBP and inhibition of either CD46 or PARP.
- In lung cancer cell lines we observed differential sensitivity to CCS1357, BET deficient lines were more sensitive (cell viability) compared to normal.
- CCS4177 is a potential first-in-class p300/CBP inhibitor for the treatment of CRPC, and potentially in the future, of tumours harbouring p300 and CBP mutations.

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