CCS1477, a novel p300/CBP bromodomain inhibitor, enhances efficacy of azacitidine and venetoclax in pre-clinical models of acute myeloid leukaemia and lymphoma

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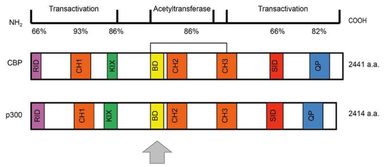
Introduction

- E1A binding protein (p300) and CREB binding protein (CBP) are two closely related histone acetyl transferases that co-activate key oncogenes such as *MYC* and *IRF4* which are relevant in a number of haematological malignancies.
- Here we describe the effects of CCS1477, a first in class orally available inhibitor of the p300/CBP bromodomains, given alone or in combination with azacitidine or venetoclax in pre-clinical models of AML and B-cell lymphoma.

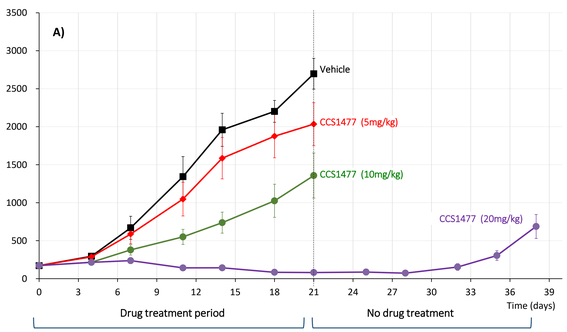
1. CCS1477 is a potent and selective inhibitor of p300/CBP bromodomains



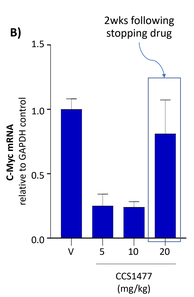
CCS1477 binds to the conserved bromo-domain of p300 and CBP

	CCS1477
p300/CBP Kd (nM)	1.3 / 1.7
BRD4 Kd (nM)	222
Selectivity	170
Bromoscan @ 1µM; 32 bromodomains (% control)	BRD4 (18%); BRD1/2/3/T (15-43%) WDR (33%)

2. Tumour regression after CCS1477 treatment in a xenograft model of AML (MOLM-16): continued inhibition following drug withdrawal

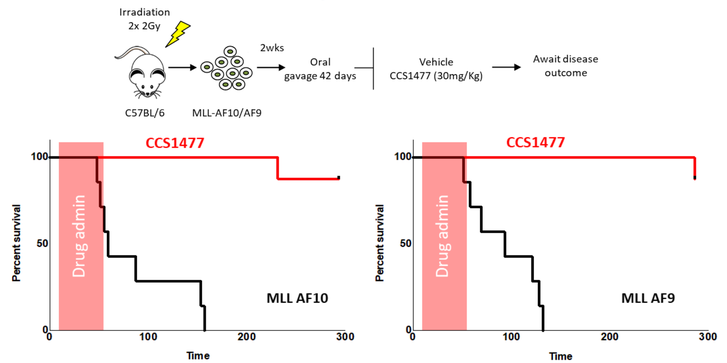


A) CCS1477 given by oral gavage once daily to MOLM-16 bearing NOD/SCID mice

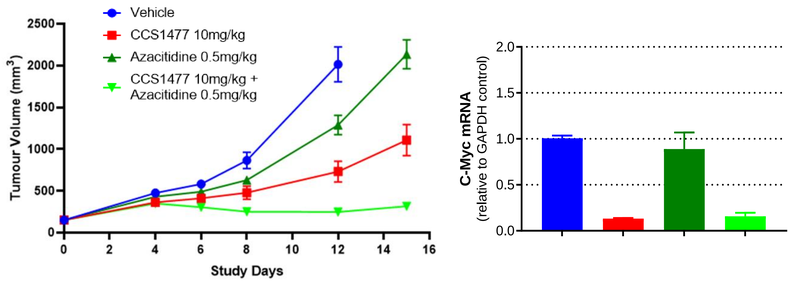


B) Impact on cMYC gene expression at d21 of treatment (5 & 10mg/kg) and at d38 following drug withdrawal at 20mg/kg

3. CCS477 prolongs survival in murine retroviral transduction and transplantation models of human AML initiated by either MLL-AF10 or MLL-AF9

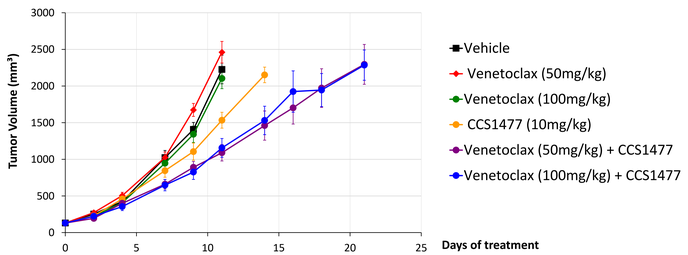


4. CCS1477 in combination with azacitidine results in superior tumour growth inhibition and a significant reduction in tumour C-Myc mRNA in MOLM-16 model



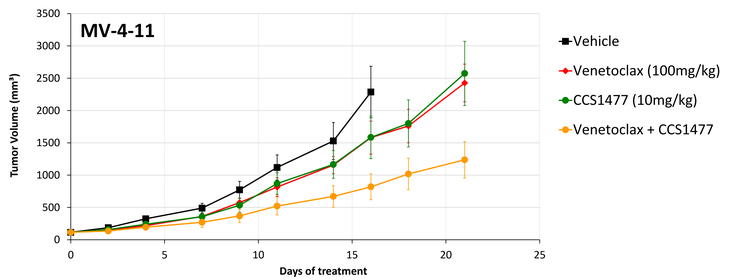
MOLM-16 bearing NOD/SCID mice were treated with CCS1477 by daily oral gavage and with azacytidine by ip injection for 5days/week.

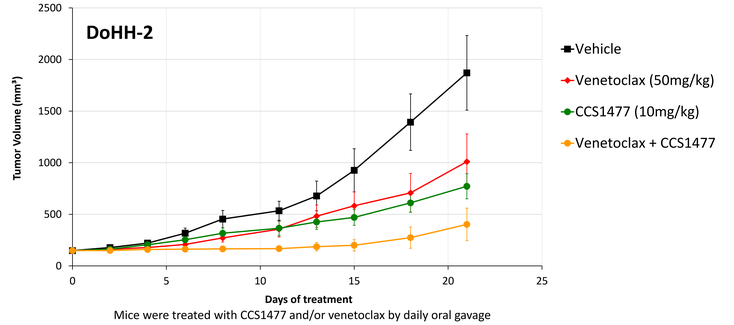
5. CCS1477 restores sensitivity to venetoclax in a venetoclax resistant MOLM-16 xenograft model of AML



MOLM-16 bearing NOD/SICD mice were treated with CCS1477 and/or venetoclax by daily oral gavage

6. Superior inhibition of tumour growth of CCS1477 in combination with venetoclax in venetoclax sensitive models of AML (MV-4-11) and B-cell lymphoma (DOHH-1)





Mice were treated with CCS1477 and/or venetoclax by daily oral gavage

Summary

- CCS1477 is a potent and selective small molecule inhibitor of the bromo-domain of p300/CBP
- CCS1477 causes tumours to regress and prolongs survival in pre-clinical models of human AML *in vivo*.
- Pre-clinical data presented here, support the clinical development of CCS1477 in combination with azacitidine and/or venetoclax in AML and B-cell lymphoma
- CCS1477 is the first p300/CBP inhibitor to be tested clinically in a Phase I/II trial of haematological malignancies, including MM, AML and NHL (NCT04068597)

Conflict of interests: Nigel Brooks, Tomasz Knurowski, Karen Clegg, Will West and Neil Pegg are employees and stockholders in CellCentric Ltd. Andrew Hughes is a stockholder in CellCentric Ltd. There are no relationships to disclose for Gary Spencer, John Chadwick or Tim Somervaille.