Introduction

- E1A binding protein (p300) and CREB binding protein (CBP) are two closely related histone acetyl transferase proteins with oncogenic roles in acute myeloid leukemia (AML) and multiple myeloma (MM).
- CCS1477 is a potent, selective and orally bioavailable p300/CBP bromodomain inhibitor, currently in Phase II clinical trials.
- Here we report the pre-clinical characterization of CCS1477 and its therapeutic application in AML and MM.

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

<table>
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<tr>
<th>Compound</th>
<th>EC50 (nM)</th>
<th>Selectivity</th>
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<tr>
<td>CCS1477</td>
<td>1.37 ± 1.7</td>
<td>170</td>
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<tr>
<td>BRD4_8D</td>
<td>222</td>
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CCS1477 binds to the conserved bromo-domain of p300 and CBP.

2. CCS1477 is a potent inhibitor of proliferation in a panel of multiple myeloma and AML cell lines in vitro

- CCS1477 causes tumour regression in a xenograft model of multiple myeloma (OPM-2); continued inhibition following drug withdrawal.

3. CCS1477 inhibits proliferation in lenalidomide resistant cell lines

- Intrinsically resistant: RPMI 8226, CP1, KMS-11, OPM-2.
- Acquired resistance: RPMI 8226, CP1, KMS-11.

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5. Superior efficacy and combination benefit of CCS1477 with standard of care therapies for multiple myeloma

6. CCS1477 inhibits proliferation, causes G1 cell cycle arrest and induces differentiation in human AML primary cells

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7. Tumour regression after CCS1477 treatment in a xenograft model of AML

- CCS1477: A novel small molecule inhibitor of p300/CBP for the treatment of acute myeloid leukaemia and multiple myeloma

Nigel Brooks, Meera Raja, Barbara Young, Gary Spencer, Tim Somervaille, Neil Pegg
CellCentric Ltd, Cambridge UK; 1Signature Discovery, Nottingham UK; 2Cancer Research UK Manchester Institute, The Christie NHS Foundation Trust, The University of Manchester, UK

Summary

- CCS1477 is a potent and selective small molecule inhibitor of the bromodomain of p300/CBP.
- Pre-clinical data presented here, support the clinical development of CCS1477 in MM and AML, either as monotherapy or in combination with standard of care therapies, incl. lenalidomide.
- CCS1477 is the first p300/CBP inhibitor to be tested clinically in a Phase II trial of haematological malignancies, including MM, AML and NHL (NCT04065897).