CCS1477, a potent and selective p300/CBP bromodomain inhibitor, is targeted and differentiated from BET inhibitors in prostate cancer cell lines in vitro

1CellCentric Ltd, Cambridge UK; 2Syngnuture Discovery, Nottingham UK; 3Northern Institute for Cancer Research, Newcastle, UK; 4Oncognition, Market Drayton, UK

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

2. Development of JQ1 resistant 22Rv1 cells

3. CCS1477 retains antiproliferative activity in JQ1 resistant 22Rv1 cells

4. Inhibitory effect of JQ1 on c-Myc gene and protein expression is abrogated in resistant cells

5. Potent inhibitory effect of CCS1477 on TMPRSS2 & KLK3 gene expression is greater vs. JQ1

6. Synergy between CCS1477 and JQ1 in parental 22Rv1 cells indicates differentiated mode of action

7. Significantly fewer genes are altered after CCS1477 vs JQ1 in parental 22Rv1 cells

Conclusions
These studies provide three lines of evidence for a differentiated mode of action of CCS1477 vs BETi:

1. CCS1477 continues to inhibit proliferation and relevant response biomarkers in a cell line that is resistant to BETi
2. There is a synergistic, rather than additive effect of combining CCS1477 with JQ1 on cell proliferation
3. Significantly fewer genes and a distinct pattern of gene change after CCS1477 vs JQ1

Collectively, these data point to a differentiated and more selective profile of p300/CBP inhibition with CCS1477