Epigenetic Therapies:
Identification and characterisation of novel dual HKMT inhibitors

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Why Dual EZH2 and EHMT2 inhibition?

- **EZH2 and EHMT2 Histone Methyltransferases are essential for cancer stem cell maintenance**
- **Existing EZH2 inhibitors have little activity in solid tumours that express wild type EZH2**

- **EZH2 and EHMT2 show increased copy number and high expression in wide variety of epithelial tumour types.**
- **SiRNA double knock down of EZH2 and EHMT2 or pharmacological inhibition of both EZH2 and EHMT2 is more biologically effective at (Curry et al 2015)**

Better biological activity

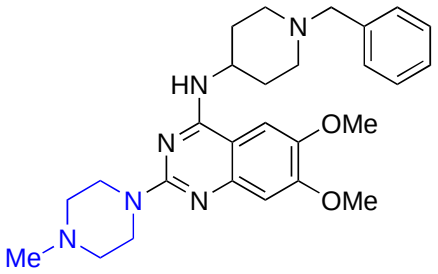
- **Potential to generate novel chemical matter with mechanism of action different from existing drugs**
- **Simpler to deliver and schedule dual inhibitor than two epigenetic drugs especially in combination studies with other therapies**

Novel drug

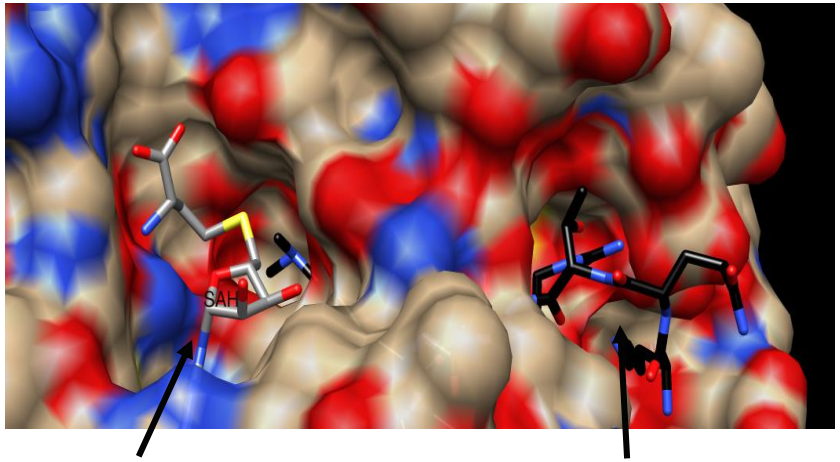
Histone Methyltransferase (HKMT) inhibitors

Dual EZH2/EHMT2 inhibitor

HKMTI-1-005



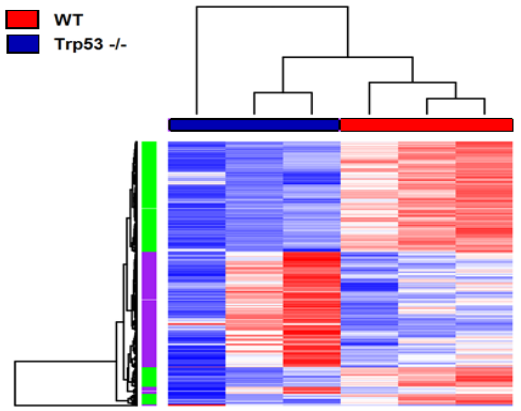
Curry, E. et al. Clin. Epigenetics ***2015****, 7:84; WO2013140148*



SAM pocket

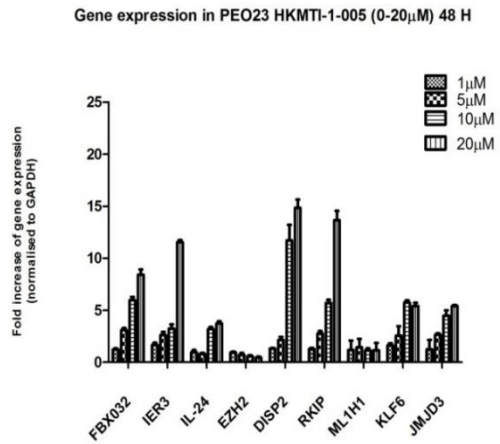
Histone pocket

ATAC-seq



- Substrate competitive, peptide binding site, dual EZH2/EHMT2 inhibitor – different mechanism of action from existing HKMT inhibitors
- Alters chromatin (H3K9me and H3K27me) and reactivates epigenetically silenced genes
- Growth inhibitory activity against ovarian, breast, lymphoma and lung tumour cells
- Synergises with PARP inhibitors and cisplatin
- Immunomodulatory activity

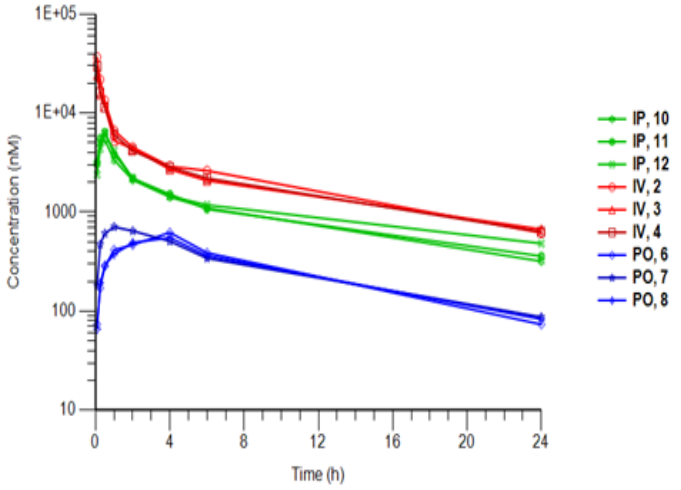
qRT-PCR



Lead compound (HKMT-1-005)

- Appropriate ADME properties –"drug like"
- Well characterised salt formulation for in vivo studies (Salt Form Solutions)
- Good pharmacokinetics
- Well tolerated in mice at pharmacodynamically active doses
- In vivo growth inhibition as single agent against some xenografts
- Identified potential stratification biomarkers for patient selection
- Synergy with molecularly targeted agents: PARP inhibitor
- Immunomodulatory activity in syngeneic ovarian cancer mouse models

A Pharmacokinetics



Isobologram