Dual-targeted BET/PI3K Inhibitors

THERAPEUTIC: Oncology

<table>
<thead>
<tr>
<th>Product Type</th>
<th>Small molecule drug candidate</th>
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<tr>
<td>Indication / ROA</td>
<td>Multiple myeloma (MM), high grade lymphoma and other cancers; injectable, oral</td>
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<tr>
<td>Target / MoA</td>
<td>Dual Inhibitor - Bromodomain and extra terminal domain (BET) proteins and Phosphoinositide-3-Kinase (PI3K); Chimeric BET/PI3K inhibitors engineered to antagonize MYC oncogene activity at both the transcriptional and protein level, while circumventing compensatory survival signaling that is initiated in response to BET single agent inhibition.</td>
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<td>Development Stage</td>
<td>Lead series discovery</td>
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| Brief Description & Differentiation | The epigenetic targets Bromodomain and extra terminal domain (BET) proteins have been identified as having a key role in activating MYC transcription. Dysregulation of MYC oncogene is a shared prognostic factor of poor response in several cancers. There are several BET inhibitors under clinical development. However, there are indications that BET inhibitor resistance rapidly emerges and that single-agent BET inhibition is not sufficient to induce sustained responses. Our novel Dual Inhibitor targeting BET and PI3K has the following features:  
  • Multi-targeted drug antagonising MYC oncogene activity at both the transcriptional and protein level.  
  • A PI3K inhibitor scaffold is fused to the BRD domain to generate a novel lead series that has demonstrated inhibition of both targets at mid to low-nM range.  
  • Avoid resistance mechanisms of selective BRD inhibitors.  
  • Potential for improved efficacy against a broad range of cancers that are driven by dysregulation of the MYC oncogene. |
| Research Team       | A/Prof Jake Shortt and Prof Phil Thompson |
| Intellectual Property | Patent to be filed around novel small molecule compositions |
| Key Publications    | Confidential                   |
| Future              | Develop lead series further to lead candidate and prove PoC efficacy and toxicity. Progress to formal preclinical and then clinical development. |

Key Data

Monash dual PI3K and BET Inhibitors demonstrates potency in vitro (Fig 1 and 2).

We are currently generating in vivo Proof of principle efficacy data for dual activity PI3K-BET inhibitor.

SEE NEXT PAGE FOR ADDITIONAL DATA:
Figure 1
A. Comparison of pro-apoptotic activity (TMRE staining) of 18D-S versus SF2523 in OPM2 human myeloma cell line (48hrs).
B. Comparison of apoptosis (TMRE staining) of 18D-S treated OPM2 human myeloma cell line vs. HS-5 bone marrow stromal cell line for 48 hours.
C. cMYC transcription levels (qPCR assay) in OPM2 cells treated with drug candidates for 2 hrs. RNASeq analysis of OPM2 cells treated with 18D-S (250nM), JQ1 (250nM) or BKM120 (1uM) for 2 hrs.
D. Principle component analysis
E. Venn diagram illustrating differentially expressed genes
F. Correlation co-efficient of JQ1 vs 18D-S
G. Enrichment of downregulated MYC signature in 18D-S treated cells.

Figure 2
A. Schematic demonstrating dual activity of Monash lead compounds (CD18D and C34D) in the context of MYC positive B-cell lymphoma.
B. Biochemical IC_{50} of CD18D and C34D vs. BD1 of BRD4 (FRET assay) and PI3Ka (Kinase Glo assay). Published IC_{50} for comparator tool compounds (JQ1, BKM120 and SF2523) are provided for reference. B1 and P1 refer to parental compounds which have been hybridised to form C18D/CD34D.
C. Cell cycle inhibitory effects of CD18D/CD34D compared to PI3K inhibition (BKM120) or BET inhibition (JQ1) in the OPM2 human myeloma cell line (48hrs treatment).
D. Apoptosis induction (Annexin V staining) comparing racemic C34D and C18D to S-enantiomer. As the interaction between C18D and C34D and BRD4 is stereoselective, S-enantiomers are predicted to be approximately twice as potent versus BET proteins.
E. Apoptosis induction (tetramethylrhodamine ester (TMRE) staining) by C18D(S) in OPM2 human myeloma cell line (48hrs).
F. Suppression of canonical PI3K phosphorylation targets (pAKT) and cMYC expression by C18D/C34D in OPM2 cells at 4 hrs. BKM120 and JQ1 are provided as comparators.