Specific BET Bromodomain inhibitors to treat disease

- Pan-BET inhibitors are currently in clinical trials for various cancers
- Novel inhibitors for specific members of the BET family have been identified
- These offer a targeted strategy over currently available compounds

Team

**Catalyst Therapeutics**
- Professor Andrew Wilks, PhD  
  - CEO

**Walter and Eliza Hall Institute**
- Chris Burns, PhD  
  - Laboratory Head, Chemical Biology division

**SYNthesis med chem**
- Xian Bu, PhD  
  - Managing Director

The opportunity

Bromodomain containing proteins are reader domains of epigenetic marks that play key roles in transcription control and chromatin remodelling. The Bromodomain (BRD) and Extra-C Terminal domain (BET) protein family consists of four members (BRD2, BRD3, BRD4 and BRDT). These ‘epigenetic readers’ bind to acetyllysine (KAc) residues on the tails of histones H3 and H4 to control gene expression.

BRD4 is required for the G2 to M phase transition of the cell cycle and regulates the transcription factor MYC. Indeed, repressing MYC through BRD4 gene knock-down or treatment with a pan small molecule inhibitor known as JQ1 appears to be highly effective in inhibiting MYC-dependent tumour growth. At least four pan-BET inhibitors have now entered clinical trials for the treatment of various tumours.

Expression of key inflammatory genes are down-regulated by inhibition of BET bromodomains, conferring protection against endotoxic shock and bacteria-induced sepsis. Because of this, there is strong evidence for targeting BET bromodomains as an approach to treat MYC-driven cancers as well as inflammatory diseases.

Whilst pan inhibitors are in clinical development, there are significant potential risks associated with pan-BET inhibition. Building on strengths in drug discovery at the Walter and Eliza Hall Institute and SYNthesis med chem, a program has been initiated to identify novel and potent inhibitors of BET bromodomains, which have greater specificity across the family. Lead compounds have already been identified with selectivity for various family members, and the team is currently undertaking further studies with these compounds to improve their selectivity and drug-like characteristics.

Catalyst Therapeutics collaborates with the Walter and Eliza Hall Institute and SYNthesis med chem on this program, where biological studies are conducted at the Institute, and medicinal chemistry design and synthesis at both SYNthesis med chem and the Institute.

The technology

- Late lead optimization is underway to further improve selectivity, potency and pharmacokinetics.
- X-ray crystallography demonstrates binding mode of the compounds.

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**Table 1. BET protein inhibition for selected compounds utilizing ALPHAscreen assay format, where red <50nM, Green >1000nM**

<table>
<thead>
<tr>
<th>First domain</th>
<th>Second Domain</th>
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<tbody>
<tr>
<td>BRD2(1)</td>
<td>BRD3(1)</td>
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Applications

▶ **Chemotherapy.** BET Bromodomain family members are implicated in many cancer types including leukemias, lymphomas, multiple myeloma and MYC-driven cancers such as certain breast cancers.

▶ **Anti-inflammatory.** Compounds identified in this program may also have potential anti-inflammatory effects.

▶ **Chemical tools.** These compounds will be instrumental to further characterizing the role of each member of the BET Bromodomain family in biology and disease.

Opportunity for partnership

Catalyst Therapeutics is seeking a partner to co-invest in the development of these novel small molecule compounds. The ultimate goal is to develop an orally available small molecule candidate and back up compounds with appropriate potency, safety and pharmacokinetic profiles. The Walter and Eliza Hall Institute and SYNthesis med chem have a successful track record in medicinal chemistry programs focused on hit-to-lead and lead optimisation.

Intellectual property

Compound structures have not been publically disclosed. An opportunity exists to generate novel intellectual property.

Figure legend

**Table 1:** BET protein inhibition for selected compounds utilizing ALPHAscreen assay format, where red <50nM, Green >1000nM.

**Figure 1:** Co-crystal structure of BRD3 (domain 1) with one of the lead compounds. Solved at the Walter and Eliza Hall Institute.

**Figure 2:** Rat pharmacokinetic study of one of the novel and potent BET inhibitors.

Collaborators

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