Specific BET Bromodomain inhibitors to treat disease

- Pan-BET inhibitors are currently in clinical trials for various cancers
- Novel inhibitors with improved selectivity within the BET family identified
- These offer a targeted strategy over currently available compounds

Team
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Background
The BET family of bromodomain containing proteins consists of BRDT, BRD2, BRD3 and BRD4. Whilst BRDT expression is restricted to the testes, BRD2-4 are ubiquitously expressed. The proteins bind to acetylated lysine residues on histones H3 and H4 where they play an important role in transcriptional control. BRD4, for example, is required for the G2 to M phase transition of the cell cycle whilst BRD2 has been shown to be involved with expression of inflammatory genes.

Genetic knock-down studies or treatment with pan-BET small molecule inhibitors indicates that deletion or inhibition of BRD4 is highly effective in inhibiting MYC-dependent tumour growth. Expression of key inflammatory genes are also down-regulated by inhibition of BET bromodomains, conferring protection against endotoxic shock and bacteria-induced sepsis.

As a consequence of the promising data reported in preclinical studies using pan-BET inhibitors, at least six pan-BET inhibitors have recently entered clinical trials. Nonetheless, there are significant potential risks associated with pan-BET inhibition, and preliminary clinical data indicates a range of adverse events and toxicities associated with the use of these compounds.

The opportunity
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 that have differential activity across the family. Lead compounds have already been identified with improved selectivity for the second bromodomain of each BET BRD, and the team is currently undertaking further studies with these compounds to further optimize these activities and understand the functional consequences of this inhibitory profile.

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

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.

Figure: BET protein inhibition for selected compounds utilising ALPHAscreen assay format, where red <50nM, Green >1000nM.
The technology

- Late lead optimisation is underway to further improve selectivity, potency and pharmacokinetics.
- X-ray crystallography demonstrates a novel binding mode of the compounds.
- Biological systems and animal models: Lead compounds will be tested for toxicity in cancer cell lines as well as their ability to inhibit production of inflammatory mediators. Compounds will then be tested in animal models of inflammation and leukemia.

Applications

- **Chemotherapy.** BET Bromodomain family members are implicated in many cancer types including leukemias, lymphomas, multiple myeloma and MYC-driven cancers.
- **Anti-inflammatory.** Compounds identified in this program may also have potential anti-inflammatory effects.
- **Chemical tools.** These compounds will be instrumental to further characterising the role of each member of the BET Bromodomain family in biology and disease.

Intellectual property

Compound structures from one chemical series have been patented, whilst a second series has not been publicly disclosed. An opportunity exists to enhance and protect novel intellectual property.

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.