Targeting BFL-1 for the treatment of cancer

- BFL-1 is a key survival factor in melanoma
- Potential to develop high affinity BFL-1 selective inhibitors
- Internationally recognised development team

Scientific team
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The opportunity
Melanoma is the fifth most common cancer in the USA, and the third most common cancer in Australia. Whilst surgery is effective for treating early stage melanoma, metastatic melanoma remains one of the most difficult cancers to cure. Recent breakthroughs in the understanding of melanoma disease progression have led to the development of targeted therapies (e.g. mutant BRAF inhibitors). However, these ultimately only have a minor impact on patient prognosis and provide essentially no likelihood of curative outcome, with all patients eventually relapsing.

Emerging evidence identifies the pro-survival Bcl-2 family member, BFL-1, as a critical factor for melanoma cells. BFL-1 is expressed at unusually high levels and this has been reported to serve as a key mechanism of resistance to currently available therapies, including mutant BRAF inhibitors.

The research team has developed a novel BFL-1-specific tool compound, and demonstrated that inhibition of BFL-1 is sufficient to kill melanoma cells in culture.

In order to capitalize on the institute’s strong track record and extensive know-how in the development of so-called BH3 mimetics designed to inhibit homologues of BFL-1, researchers have recently initiated a high-throughput chemical screen to identify small molecules inhibitors of BFL-1.

The technology
While a number of compounds have been developed that target its homologues, so far compounds that target BFL-1 have proved elusive.

A suitable high-throughput screening assay has been established, and candidate molecules identified will be further validated. Key resources that have been developed by the research team include:
1) The ability to produce purified BFL-1 in quantities and purity suitable for high-throughput screening, hit validation and structural studies
2) A tool peptide-based compound that is selective for BFL-1, and has been employed to identify BFL-1 dependent cancer cell lines for hit validation studies
3) Genetically engineered cell lines that will be useful for hit validation studies
4) Genetically engineered mouse models that will be useful for in vivo candidate evaluation

![Figure 1. Selective targeting of BFL-1. Bfl1sel tool compound selectively binds BFL-1 with high affinity](image-url)
Applications

In addition to melanoma, numerous other cancers exhibit abnormally elevated levels of BFL-1 and may also respond to treatment with BFL-1 inhibitors, such as B-cell lymphoma and T-cell lymphoma.

Opportunity for partnership

The Walter and Eliza Hall Institute seeks a partner to co-invest in the development of novel small molecule compounds targeting BFL-1. The ultimate goal is to develop a small molecule clinical candidate as well as back-up compounds with appropriate potency, safety and pharmacokinetic profiles.

The Walter and Eliza Hall Institute is extensively experienced and has a successful track record in drug discovery programs focused on high-throughput chemical screening, hit-to-lead and lead optimisation. The institute has played a critical role in the development of several BH3-mimetics including ABT-199, currently in clinical trials for the treatment of chronic lymphocytic leukaemia (CLL).

Intellectual property

Compound structures have not been publicly disclosed. An opportunity exists to generate novel composition of matter intellectual property.

Key publications


Figure legend

**Figure 1:** Selective targeting of BFL-1. Bfl1sel tool compound selectively binds BFL-1 with high affinity.

**Figure 2:** Bfl1sel tool compound efficiently kills melanoma cell lines in vitro, including those that are relatively insensitive to BRAF inhibition.