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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Background

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 a 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 (Figure 1), and demonstrated that inhibition of BFL-1 is sufficient to kill melanoma cells in culture (Figure 2).

In order to capitalise on the institute’s strong track record and extensive know-how in the development of BH3 mimetics designed to inhibit homologues of BFL-1, researchers have recently completed two screens to identify 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.

Researchers at the Walter and Eliza Hall Institute have used two approaches to identify BFL-1 inhibitors:

- High-throughput screening. Using the institute’s 114,000 lead-like compound library, a screen has been completed. Scientists are currently triaging the hit compounds for further investigation.

- Fragment-based screening. This screen has also been completed, which has yielded a number of compounds worthy of further investigation.

Capabilities and resources to enable high quality hit-to-lead and lead optimisation studies are at available at the institute, which include:

1. The ability to produce purified BFL-1 in quantities and purity suitable for hit validation and structural studies
2. A tool peptide-based compound selective for BFL-1, which has been employed to identify BFL-1-dependent cancer cell lines for hit validation
3. Genetically engineered cell lines
4. Genetically engineered animal models
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.

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

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 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 phase 3 clinical trials for the treatment of chronic lymphocytic leukaemia (CLL).

The experienced multidisciplinary team working on this project includes the Cell Death and Survival laboratory at the Olivia Newton-John Cancer Research Institute. Integrated within a hospital environment, these researchers work together with clinicians for the ultimate benefit of patients with cancer.

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.*

Walter and Eliza Hall Institute of Medical Research
The Walter and Eliza Hall Institute is Australia’s longest-serving medical research institute, celebrating its centenary in 2015. Our multidisciplinary research teams are focused on solving complex biological questions, and effectively linking laboratory research to the clinic. With a strong collaborative focus, the institute is a founding member of Biomedical Research Victoria, Cancer Trials Australia, BioGrid Australia and the Victorian Comprehensive Cancer Centre.

Research
• 750 research staff trained nationally and internationally
• 81 research laboratories
The institute’s scientists are driving innovative programs aimed at understanding, preventing and treating:
• Cancer: especially leukaemia, lymphoma, breast cancer, bowel cancer, ovarian cancer, lung cancer, pancreatic cancer, stomach cancer
• Immune disorders: including diabetes, rheumatoid arthritis, coeliac disease, rheumatic fever and other inflammatory conditions
• Infectious diseases: focusing on malaria, HIV, tuberculosis and hepatitis viruses

Research outcomes
• More than 300 publications annually
• 74% of publications in biomedical journals with an impact factor >15
• 34% of publications in the top 10% of their field

Strong translational focus
• Discovery pipeline fed by more than 300 projects
• Institute research is the basis of more than 100 clinical trials, and has resulted in 4 start-up companies and 5 spin-out companies
• Institute research has benefited more than 20 million people worldwide

Opportunities for partnership
• Therapeutics
• Biomarkers and diagnostics
• Unique pre-clinical models
• Access to platform technologies including
  - bioinformatics
  - clinical translation centre
  - drug discovery including high-throughput screening and medicinal chemistry
  - systems biology including proteomics

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