Novel anti-schistosomal drugs

- More than 200 million people infected with schistosomes
- BH3 mimetics (pro-apoptosis drugs) in clinical trials for cancer therapy
- Program to develop first-in-class anti-infective therapeutics: BH3 mimetics selective for schistosomes

Scientific team

Douglas Fairlie, PhD
Structural Biology division

Erinna Lee, PhD
Structural Biology division

Associate Professor Guillaume Lessene, PhD
Chemical Biology division

The opportunity

Globally, more than a billion people are infected with parasitic worms (helminths), leading to a high degree of death and morbidity. Infection with schistosomes, the worms that cause schistosomiasis, afflicts more than 200 million people worldwide, leading to approximately 300,000 annual deaths in Africa alone, and ranking this disease alongside other major public health burdens such as malaria and tuberculosis. Currently, schistosomiasis is treated predominantly with a single drug (praziquantel), but due to the heavy reliance on this compound, there is growing concern about the development of resistance, which has been observed in the laboratory as well as in the field. As such, novel treatments are required.

Scientists at the Walter and Eliza Hall Institute are developing a novel therapeutic to treat schistosomiasis.

The technology

As part of worldwide efforts to identify potential new targets for anti-schistosome drugs, the genomes for the three major disease-causing species of schistosome were sequenced. Walter and Eliza Hall Institute researchers searched through the sequence databases, and identified all of the major components of a Bcl-2-regulated programmed cell death (apoptosis) pathway. This was examined in vitro through biochemical and expression/co-expression studies in mammalian cells, and it was discovered that the schistosome Bcl-2-regulated pathway is structured similarly to the mammalian Bcl-2 pathway.

This is a significant finding as human Bcl-2 pro-survival proteins have been targeted with small molecule drugs called “BH3-mimetics” in cancer therapy – these compounds are pro-apoptotic, and are currently being evaluated clinically in patients with cancers that overexpress Bcl-2. Thus, it is conceivable that similar drugs targeting the schistosome Bcl-2 pro-survival protein (sBcl-2) could represent a new strategy for eliminating the parasites.

To circumvent unwanted activation of apoptosis in cells of the human host, scientists are developing a schistosome-specific BH3 mimic.

Preliminary experiments demonstrated that purified sBcl-2 bound to a number of well-characterised BH3-mimetics with affinities <1 μM. The researchers have also generated high-resolution X-ray crystallographic structural data showing binding of sBcl-2 to one of these compounds (IC₅₀ ~200 nm).

Taken together, it presents as an excellent starting point for a medicinal chemistry campaign.

Applications

While the primary focus is on targeting sBcl-2 in schistosomes, there is the potential for application in other helminth-based diseases.

Opportunity for partnership

The Walter and Eliza Hall Institute is seeking a partner to co-invest in the development of schistosome-specific BH3 mimic compounds. The ultimate goal is to develop an anti-schistosomal drug that possesses appropriate potency, safety and pharmacokinetic profiles.

The Walter and Eliza Hall Institute is a world leader in apoptosis research, and has a proven track record in medicinal chemistry programs focused on hit-to-lead and lead optimisation.

Intellectual property

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

Key publications


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 and 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
• More than 470 collaborative partners across 120 cities in 43 countries

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

Contacts

Dr Julian Clark
Head Business Development
jclark@wehi.edu.au

Dr Kurt Lackovic
Business Development Manager
lackovic@wehi.edu.au

Walter and Eliza Hall Institute of Medical Research

1G Royal Parade Parkville
Victoria 3052 Australia
+61 3 9345 2555
www.wehi.edu.au/businessdevelopment