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
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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 over-express 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 mimetic.

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.

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.
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 mimetic 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
