Development of a novel therapeutic to treat malaria

- The malaria protease, plasmepsin V, is essential for parasite survival

- Plasmepsin V is a novel druggable target. X-ray crystal structure obtained

- Campaign to develop potent drug-like inhibitors of Plasmepsin V

Scientific team

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The opportunity

Several hundred million people are infected with malaria annually, resulting in approximately one million deaths per year and the causation of profound social-economic problems. There is currently no vaccine, and drug resistance is rapidly increasing.

Malaria is caused by the Plasmodium parasite, the most virulent form, \textit{P. falciparum} accounts for 70\% of infections, while \textit{P. vivax} is responsible for post-treatment symptomatic relapse and accounts for 30\% of known infections. Malaria parasites survive inside human red blood cells by exporting hundreds of proteins into the erythrocyte to remodel it. Approximately 450 proteins are exported by trafficking through the parasite Endoplasmic Reticulum (ER) and possess a N-terminal export motif, termed the Plasmodium export element (PEXEL), which targets the proteins to the erythrocyte. In order for proteins to be correctly exported, the PEXEL motif must be processed by an ER-resident aspartic acid protease called Plasmepsin V (PMV). If processing of PEXEL proteins does not take place, they are not exported and accumulate inside the parasite. Thus, blocking protein export offers a potential therapeutic mechanism to prevent survival and transmission of malaria parasites.

Researchers at the Walter and Eliza Hall Institute have identified that PMV is critical for the export of proteins from the malaria parasite. As such, development of therapeutics inhibiting PMV potentially leads to novel anti-malarial therapeutics.

The technology

Institute researchers have developed probes that mimic the PEXEL substrate and are highly potent and selective inhibitors of PMV. The mimetics display potent inhibition of PMV from both \textit{P. falciparum} and \textit{P. vivax} with negligible off-target activity against human proteases, confirming that the export pathway is conserved in Plasmodium species. The researchers have obtained an X-ray crystal structure of PMV bound to a probe, which shows that PMV has an exquisitely refined substrate specificity. For the first time, the researchers have demonstrated that the treatment of \textit{P. falciparum} parasites in culture with the small molecule probe causes: (i) a reduction in PEXEL processing and protein export; and (ii) parasite death. Together, it reinforces PMV as a prime anti-malarial target.

These proof-of-principle experiments have led to two projects:

- The PEXEL mimetic probe is currently being further optimised by a structure-guided approach, and will be used to further understand the role of PMV in liver and transmission stages of the parasites’ lifecycle. Currently, analogues are being synthesised and tested \textit{in vitro}.

- High-throughput screening of a library of compounds that possess anti-malarial properties (~13,500) was performed to identify inhibitors of PMV. The screening cascade that was employed identified a single drug-like class of 8 compounds. Medicinal chemistry efforts have established an early structure activity relationship, and researchers are currently focusing on improving the potency of the lead class.

Applications

Malaria is a global public health burden, with worldwide infections into the hundreds of millions, and deaths of approximately one million people annually.

Opportunity for partnership

The Walter and Eliza Hall Institute is seeking a partner to co-invest in development of the drug-like series that will not only target blood stage malaria, but potentially liver and transmission stages of malaria.

The ultimate goal is to develop an anti-malarial drug that possesses the appropriate potency, safety and pharmacokinetic profiles.

The institute is a world leader in malaria research and has extensive experience
and expertise in the identification and characterisation of novel drug targets. Moreover, the institute has a successful track record in medicinal chemistry programs focused on high-throughput screening, 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**


**Figure legend**

Figure 1: PMV is expressed in the ER (perinuclear) of liver stage *P. falciparum* parasites. Liver sections from infected humanized mice 7 days post-infection probed with antibodies to PMV (green), the PV membrane protein, EXP1 (red), and the nucleus, DAPI (blue).

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**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

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