Novel anti-HIV compounds: frameshift modulators

- Unique approach to target HIV: HIV gene translation
- Targeted mechanism is HIV frameshifting
- Compounds that modulate HIV frameshifting identified via a novel HTS campaign

Scientific team

Brad Sleebs, PhD
Chemical Biology division

Helene Jousset, PhD
Systems Biology and Personalised Medicine division

Professor Warren Tate, PhD
University of Otago, School of Medical Sciences

The opportunity

Human immunodeficiency virus (HIV) is a virus that causes acquired immunodeficiency syndrome (AIDS). AIDS-related illnesses are one of the leading causes of deaths worldwide. The current standard of care for HIV infections is to use drugs that control viral load, whereby the viral life cycle stages are targeted (i.e. binding; fusion; reverse transcription; integration; budding; and maturation). Due to the high mutation rate of HIV, drug resistance presents as a major issue.

Researchers at The Walter and Eliza Hall Institute and University of Otago are developing a novel class of drugs targeting a critical mechanism in HIV survival and replication. HIV uses a rare genetic mechanism termed ‘frameshifting’ to change the reading frame of its mRNA, allowing it to regulate the ratio of the structural and enzymatic proteins that are produced. The correct ratio is essential for viral infectivity as the incorrect proportion leads to a dramatic reduction in infection. The frameshift mechanism relies upon: (i) a slippery sequence for the translating ribosome to slip on; and (ii) a structural feature (stem loop). Both of these RNA elements are very highly conserved and mutations in these sequences have not been described, indicating that drug resistance via this mechanism could be very low. Thus far, the only human gene known to undergo frameshifting in vivo is the putative developmental gene PEG10. However, reports have yet to demonstrate that PEG10 is expressed in adult tissue.

The Walter and Eliza Hall Institute and University of Otago have expertise in translational biology, high-throughput screening and medicinal chemistry. The project team has identified compounds that modulate the frameshift mechanism. To date:

- Compounds confirmed to modulate frameshifting
- Compounds have drug-like properties
- Compounds are synthetically tractable
- Compounds have limited cytotoxicity
- Hit-to-lead stage, ripe for further development

Applications

- HIV: Globally, approximately 33 million people are infected with HIV and numbers are projected to increase over the coming years.
- Other viruses that depend upon frameshifting. Compounds identified in this screen may also have the potential to inhibit other viruses.
- Discovery tools. For use in identifying the mechanism and regulation of translational frameshifting.

The technology

The assay employed to quantify frameshifting was a dual Firefly and Renilla luciferase reporter gene system: the downstream reporter is expressed only as a fusion protein with the upstream reporter if the frameshifting event takes place (Figure 1). Through screening of 114,000 lead-like small molecules, a number of compounds (both frameshift inhibitors and enhancers; Figure 2) were confirmed to modulate frameshifting.

IMOE software analysis demonstrated that the hit compounds have inherent lead-like properties according to Lipinski parameters. Upon analysis of the modulators, 8 singletons and 4 structural classes were identified, whereby an early structural-activity relationship pattern can be observed. The hit singletons and the hit classes are synthetically tractable.

Figure 1: Reporter construct used to screen for frameshift modulators

Figure 2: Examples of compounds able to modulate frameshift activity
Opportunity for partnership
The Walter and Eliza Hall Institute and University of Otago are seeking a partner to co-invest in the development of novel small molecule compounds identified to modulate HIV frameshifting. The ultimate goal is to develop an orally available small molecule candidate and back-up compounds with the appropriate potency, safety and pharmacokinetic profiles. The Walter and Eliza Hall Institute has a successful track record in medicinal chemistry programs focused on hit-to-lead and lead optimisation.

Intellectual property
The intellectual property regarding the dual-fluorescent reporter construct and assay for measuring translational recoding is protected (WO/2007/027106). Compound structures have not been publicly disclosed. An opportunity exists to generate novel composition of matter intellectual property.

Figure legend
Figure 1: Reporter construct used to screen for frameshift modulators. The downstream reporter (Firefly Luciferase) is expressed only as a fusion protein with the upstream reporter (Renilla Luciferase) if the frameshifting event takes place.

Figure 2: Examples of compounds able to modulate frameshift activity. (A) frameshift enhancer; (B) frameshift inhibitor. The frameshift activity (% of WT) of the cell line containing the HIV-1 frameshift element is indicated by black bars and the control mutagenized cell-line firefly activity (%) indicated by striped bars.

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

Walter and Eliza Hall Institute
Discoveries for humanity