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Novel anti-HIV compounds – frameshift modulators

- Highly conserved HIV target
- Ribosomal frameshifting critical for survival of HIV
- Compounds that modulate HIV frameshifting identified

Lead scientists

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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 death 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 WEHI and UoO 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. This critical ratio is essential for viral infectivity as the incorrect proportion leads to a dramatic reduction in infectiousness. 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, suggesting that the frameshifting mechanism of HIV is a viable target. Currently, drug therapies that target frameshifting have not reached market.

WEHI/UoO experts in HIV and medicinal chemistry have identified compounds that modulate the frameshift mechanism. To date:

- 18 compounds confirmed to modulate frameshifting
- Compounds have drug-like properties
- Compounds are synthetically tractable
- Compounds have limited cytotoxicity
- Hit to lead stage.

The Technology

The assay for quantifying frameshifting was the 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 113,000 lead-like compounds, 18 compounds were confirmed to modulate frameshifting (15 inhibitors and 3 enhancers; Figure 2).

Figure 1. Reporter construct to screen for frameshift modulators

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MOE software analysis demonstrated that the hit compounds have inherent lead-like properties according to Lipinski parameters. Upon analysis of the 18 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.

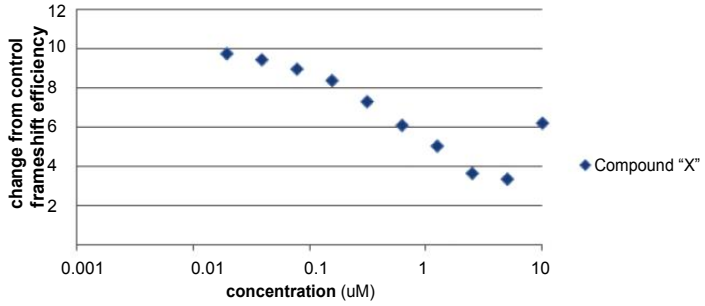

Figure 2. Example of a frameshift inhibitor

Applications

Molecules targeting the frameshift mechanism may be applicable for:

- **HIV:** Globally, approximately 33 Million people are infected with HIV and numbers are projected to grow.
- **Other viruses that depend upon frameshifting**. Compounds identified in this screen may also have the potential to inhibit other viruses, for example, coronavirus (e.g. SARS), deltaretrovirus (e.g. Human T-lymphotropic virus 1) and astrovirus (e.g. Human astrovirus 1).
- **Discovery tools.** For use in identifying the mechanism and regulation of translational frameshifting.

Opportunity for Partnership

WEHI and UoO are seeking a partner to co-invest in development of the novel small molecule compounds identified in the screen. An extensive hit-to-lead program is in place to ascertain compounds suitable for lead optimisation studies. The ultimate goal is to develop an orally available small molecule candidate and back-up compounds with the appropriate potency, safety and pharmacokinetic profile. WEHI 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 (PCT/NZ2006000222).

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

Figure Legend

Figure 1: Reporter construct 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: Example of a frameshift inhibitor. Compared to control, compound "X" demonstrated a decrease in frameshift efficiency.

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