Drug therapy for dengue fever

Monash University researchers have discovered a ‘first in class’ and clinically de-risked drug candidate for treating and/or preventing dengue fever and its more severe form – dengue haemorrhagic fever.

**Benefits over existing treatments**
- ‘First in class’ dengue drug
- Potential i.v. therapeutic for dengue haemorrhagic fever
- Potential oral prophylactic for dengue fever
- Clinically de-risked

**Background**
Dengue fever is an infectious tropical disease caused by the transmission of dengue virus by several species of mosquito within the genus Aedes.

The incidence of dengue fever has increased dramatically since the 1960s, with around 390 million people infected annually and nearly half of the world’s population currently at risk. The number of infections is increasing every year.

The virus can be classified into five serotypes based on antibody reactivity. An initial infection with one serotype usually has flu-like symptoms, offering lifelong immunity to that serotype. However, it rarely provides immunity to other serotypes, and subsequent infection with a different serotype increases the risk of a patient developing severe complications (dengue haemorrhagic fever).

An estimated 500,000 people with dengue haemorrhagic fever require hospitalisation each year, a large proportion of whom are children, leading to approximately 20,000 deaths.

Dengue fever is a pure unmet medical need. Current treatment consists of using either oral or intravenous rehydration for mild or moderate disease, and intravenous fluids and blood transfusion for more severe cases.

**The opportunity**
Monash researchers, Professor David Jans, Dr Johanna Fraser and Dr Kylie Wagstaff have recognised that the synthetic retinoid derivative N-(4-hydroxyphenyl) retinamide (4-HPR; also known as Fenretinide), is efficacious in a dengue viremia mouse model, turning 100% lethality into a 70% survival rate at sub-optimal doses (refer Figure 1).

The researchers identified 4-HPR/Fenretinide through a novel in vitro screening approach, and have characterised novel ‘mechanisms of action’ by which Fenretinide imparts its efficacy on dengue.

4-HPR/Fenretinide is a known drug that has been investigated for potential use in the treatment of cancer, as well as in the treatment of a number of other indications including cystic fibrosis and rheumatoid arthritis. It is well tolerated clinically with mild and reversible side effects including skin dryness and night-blindness when used at higher doses for chronic treatments.

Currently, 4-HPR/Fenretinide is in 2 clinical trials and is being administered orally and as an injectable. These routes of administration match its potential clinical utility either as an oral prophylactic/therapeutic for treatment of dengue fever, or as an injectable for dengue haemorrhagic fever patients.

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Method of viral inhibition

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Figure 1. 4-HPR protects mice against a lethal challenge with dengue virus. AG129 mice (Schul et al., JID, 2007) were dosed once (QD) or twice (BID) daily with 20 mg/kg of 4-HPR for 5 days, starting at day 0. Mice were scored for viability until day 10 (10 mice per VC, BID and QD groups; VC – vehicle control).