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Nuclear transport inhibitors alter capsid sub-cellular localization and replication of *Venezuelan Equine Encephalitis* virus and related new world Alphaviruses

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New world alpha-viruses such as *Eastern, Venezuelan* and *Western Equine Encephalitis* Viruses (EEEV, VEEV and WEEV) cause high mortality and morbidity in equines and humans and are characterized by a febrile illness that may progress into encephalitis. The centers for disease control and prevention consider all three viruses Category B agents due to their ease of weaponization and the lack of licensed vaccines or therapeutics. The VEEV structural capsid protein blocks nuclear import in mammalian cells, most likely by forming a trimeric complex with the host nuclear import (importin α/β1) and export (CRM1) machinery. This complex sits inside the nuclear pore comples, the only transit for protein movement between cytoplasm and nucleus and prevents host protein movement, thus inhibiting the host anti-viral response, possibly due to its complexing with the host CRM1 and importin α/β1 nuclear transport proteins. Inhibition of viral protein nuclear transport is a rapidly growing area of investigation and hence nuclear transport inhibitors were investigated for their effects on capsid. Utilizing numerous transport inhibitors and a combination of *in vitro* protein binding assays with advanced quantitative confocal microscopy of transfected and infected cells as well as viral replication assays we demonstrate that VEEV capsid nuclear transport is a viable target for therapeutic intervention, resulting in reduced viral replication. Similarly other New World alpha viruses are also susceptible to these compounds suggesting for the first time that a pan-antiviral therapeutic may be possible.

Biography

Kylie M Wagstaff completed her PhD in 2007 at Monash University (Melbourne) where she remained for her Post-doctoral studies. She is presently an ARC Australian Post-Doctoral Research Fellow and manages a small research group. Her research focuses on the transport of proteins into and out of the eukaryotic cell nucleus and its therapeutic applications, including the development of inhibitors of this process as anti-viral agents and how the nuclear transport machinery may be exploited for drug delivery. She has >30 peer-reviewed publications in eminent journals (H-factor of 16) and is a recipient of numerous prestigious awards/prizes.

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