**Brains, Bugs and Biocontainment: Applying novel stem cell derived neuron models to investigate the biology of highly pathogenic viral diseases in the human brain.**

Dearnley, M.[1], Gödde, N.[1], Sundaramoorthy, V.[1], Green, D.[1], Monaghan, P.[1], Dups, J.[1], Farr, R.[1], Chatterton, R.[2], Clayton, B.[1], Klein, R.[1], Todd, S.[1], Rootes, C.[1], Stewart, C.[1], Cowled, C.[1], Bingham, J.[1], Laslett, A.[2] and O'Brien, C.[2]

[1] CSIRO Australian Animal Health Laboratory, Australia, [2] CSIRO Manufacturing, Australia

Infectious viral disease is a leading cause of morbidity and mortality worldwide and threatens social, economic and food security. In the 2017 review of priority diseases, the World Health Organization determined that there is an urgent need for research around the *Henipavirus*es, including Hendra virus (HeV) which is endemic to Australia [1]. HeV cause a flu-like syndrome in animals and humans with a 40-70% mortality rate. The virus also causes infection of the brain that disrupts the structure and function of neural cells. This leads to severe acute symptoms and/or long term disability in survivors [2-3]. However, much of the basic biology of HeV infection in the brain is still not understood. To better manage this highly infectious pathogen, there is a critical need for improved research models that will expedite our understanding of the virus to help us combat future outbreaks.

For practical and ethical reasons, it is often not feasible to develop interrogation models of neuronal infection in animals. Furthermore, our data indicates that the pathology of laboratory animals, primary cell culture and continuous cell lines show significant differences in host cell response, viral protein localisation, replication and budding. Hence, they may not accurately represent human infection. To overcome potential species-specific differences in host cell pathology, we have developed and characterised a novel model of HeV infection in neurons derived from human induced pluripotent and embryonic stem cell lines. By complementing molecular techniques with microscopy analysis at the AAHL biocontainment imaging facility, we have optimised experimental conditions for modelling HeV infection in stem cell derived culture systems to more accurately replicate HeV infection within the human brain. Our results show that human stem cells, neural progenitor cells and differentiated neurons are susceptible to HeV infection. Ultrastructural rearrangements within host cells are present in concert with a previously undescribed pattern of the virus assembly. Using a chamber-well culture system and high-resolution fluorescence microscopy, we have imaged infections of neuron cell bodies and analysed virus transmission along individual axons. This system is enabling us to further investigate the mechanism of neuron to neuron virus transmission within the brain.

This novel stem cell derived neuron model is also being utilised as a platform with which to identify microRNA biomarkers of pre-symptomatic and neuronal virus infection. In addition, we are expanding the application of this novel stem cell model to analyse the biology of other neurotropic viruses including Rabies virus and West Nile Virus. This research will enable a better understanding of a wide range of neurotropic viruses that threaten our health and economies and improve preparation for public health emergencies.

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