

Title: Characterisation and inhibition of nsp14, a potential pan-coronavirus target

Emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to the Covid-19 pandemic, causing more than 600 million infections and 6.5 million deaths worldwide. Although vaccines are available that reduce the risk of severe symptoms, there is still a clear need for effective antiviral treatments for Covid-19 and for potential future coronavirus outbreaks. Nsp14 is a proofreading enzyme with exoribonuclease activity (ExoN), which is essential for high fidelity replication of SARS-CoV-2, and also methyltransferase activity which is responsible for methylation of RNA caps. Nsp14 is highly conserved in sequence across coronaviruses, making it an attractive target for pan-coronavirus drug discovery. With the final aim of developing small molecule inhibitors of nsp14, we biochemically characterised both nsp14 activities and interactions with its cofactor, nsp10. Evaluation of single point mutations on both nsp14 activities, supported by virology studies, has demonstrated the essentiality of the ExoN activity. We also investigated and further characterised literature inhibitors. Our results suggest that reduction of nsp14 ExoN activity significantly reduces the viability of SARS-CoV-2, making it a favourable pharmacological target for development of an antiviral therapeutic against SARS-CoV-2 infection.

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