CHEM 280 & CHEM 180H SEMINAR SERIES

Small Molecule Activation and Inhibition of Viral Polymerases: A Journey From RSV to Nipah Virus

Presented by

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Noon to 12:50 p.m., Ag Mechanics, Room 102

Abstract

Human respiratory syncytial virus (RSV) is a negative-sense RNA virus and a significant cause of respiratory infection in infants and the elderly. Limited vaccines and antiviral therapies are available for the treatment of RSV. ALS-8176 is a first-in-class nucleoside prodrug inhibitor of RSV replication. ALS-8112, the parent molecule of ALS-8176, undergoes intracellular phosphorylation, yielding the active 5'-triphosphate metabolite. The host kinases responsible for this conversion are not known. Therefore, elucidation of the ALS-8112 activation pathway is key to further understanding its conversion mechanism, particularly given its potent antiviral effects. We identified the activation pathway of ALS-8112 and showed it is unlike other antiviral cytidine analogs. We then used these findings to investigate a class of emerging RNA viruses, which share common replication machinery to RSV, but their mechanisms of RNA biosynthesis activities are unknown. To study this emerging class of viruses, including polymerase structure and function, we expressed an active, recombinant Nipah virus (NiV) polymerase. We identified conserved sequence elements driving RNA synthesis activities. The lack of available antiviral therapy for NiV prompted us to identify two clinically relevant nucleotide analogs as inhibitors of NiV polymerase. This work illustrates important functional differences yet remarkable similarities between the polymerases of non-segmented negative-strand RNA viruses.

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