New host-directed approaches against emerging viral infections

Rainer Koenig (oral presentation)

18 April 2026

ESCMID 2026, Munich, Germany

Host-directed antivirals (HDAs) represent a promising strategy for combating emerging and re-emerging viral infections by targeting cellular pathways required for viral replication rather than virus-specific proteins. Unlike direct-acting antivirals (DAAs), HDAs offer the potential for broader antiviral activity, reduced susceptibility to resistance, and improved pandemic preparedness. However, despite numerous preclinical studies, only a limited number of HDAs have advanced into clinical practice due to concerns regarding cytotoxicity, target specificity, and insufficient clinical validation.

This presentation summarizes current developments in host-directed antiviral research and introduces computational approaches for identifying novel therapeutic targets. Genome-wide knockout/down screens, protein–protein interaction studies, and single-cell transcriptomics provide valuable resources for host dependency factor (HDF) discovery, although individual screening studies show remarkably poor overlap at the gene level. Integrating these data at the pathway level substantially improves consistency, providing a robust foundation for machine learning approaches that prioritize host targets across multiple datasets. Using experimentally validated HDF as benchmark data, a machine learning framework was developed by the group of the speaker to prioritize candidate host targets. This approach identified the β-catenin/CBP signaling axis as a promising antiviral target. Experimental validation demonstrated that the β-catenin/CBP inhibitor PRI-724 potently suppresses SARS-CoV-2 infection in cell lines and primary bronchial epithelial cells, while also exhibiting activity against additional RNA and DNA viruses, suggesting broad-spectrum antiviral potential. Finally, the presentation highlights drug delivery as a frequently overlooked determinant of successful HDA translation. A systematic comparison of antiviral compounds tested in conventional cell lines versus primary cell models revealed that compounds with poor clinical performance are often associated with high delivery risk, emphasizing the importance of optimized delivery strategies alongside target identification. Overall, integrating large-scale functional genomics with machine learning and rigorous experimental validation provides a powerful framework for discovering broad-spectrum host-directed antivirals. Together with improved drug delivery technologies, these approaches may substantially strengthen antiviral preparedness for future viral outbreaks and pandemics.