Novel antiviral strategies based on inhibition of viral entry into host cells: the case of SARS-CoV-2 and Influenza A Virus

Rafał Nowak

Summary

Respiratory infections are among the leading causes of death worldwide, with pathogens such as influenza A virus (IAV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) being the most common culprits. For a virus to infect a host cell and begin its replication cycle, it must first bind to a receptor on the cell surface. The virus then enters the cell, often via endocytosis, where it releases its genetic material into the cytoplasm. Viruses, such as SARS-CoV-2 and IAV, rely on host cell factors to facilitate entry and initiate infection. Therefore, inhibiting these host cell factors represents a promising strategy for developing highly effective antiviral therapies, which is crucial for controlling the spread of newly emerging viruses with epidemic or pandemic potential.

The goal of this dissertation was to explore various therapeutic strategies aimed at inhibiting viral entry into host cells, thereby disrupting the replication cycle of newly emerging respiratory viruses. This dissertation is based on three original scientific publications, each presenting a different, innovative method to block viral entry into host cells.

The first publication, *Novel Molecular Consortia of Cannabidiol with Nonsteroidal Anti-Inflammatory Drugs Inhibit Emerging Coronaviruses' Entry* (**Pawełczyk A.*, Nowak R.*, et al., "Pathogens", 2023**), demonstrated that conjugates of cannabidiol (CBD) with nonsteroidal anti-inflammatory drugs (NSAIDs) could inhibit the first step in the SARS-CoV-2 replication cycle. The CBD-Naproxen and CBD-Ibuprofen conjugates reduced SARS-CoV-2 entry into cells more than CBD, by disrupting the interaction between the spike protein of SARS-CoV-2 and the ACE2 receptor on the host cell surface.

The second publication, *TMPRSS2-specific antisense oligonucleotides inhibit host cell entry of emerging viruses* (**Nowak R., et al., "Virology", 2024**), identified the secondary structure of *TMPRSS2* mRNA, which served as the basis for designing antisense oligonucleotides (ASOs). These ASOs effectively silenced *TMPRSS2* gene expression in host cells. Consequently, a marked reduction in SARS-CoV-2 entry and IAV replication was observed. These results confirmed that TMPRSS2 is not only essential for efficient viral infection but also represents a promising target for gene expression-based antiviral therapies.

The third publication, *Organometallic–Erlotinib Conjugates Active against Lung Cancer Cells and as Emerging Virus Entry Inhibitors* (**Biegański P.*, Gazecka M.*, Nowak R., et al., "Organometallics", 2024**), presents a novel approach using erlotinib conjugates with organometallic residues. These hybrid compounds reduced the effectiveness of SARS-CoV-2 and IAV infections by indirect inhibiting the TMPRSS2-dependent activation of viral surface proteins. In addition, within this publication, we showed a novel TMPRSS2 interactor, i.e. EGFR, which have potential as other novel antiviral.

The findings from this dissertation highlight the high efficacy of various strategies aimed at blocking viral entry into host cells by inhibiting host cell factors function and/or activity. These studies open up new possibilities for the development of broad-spectrum antiviral therapies targeting common molecular mechanisms used by different respiratory viruses. The compounds and therapeutic approaches identified in this research could serve as the foundation for further preclinical and clinical studies on new antiviral drugs.