Article type: Editorial

Home Page URL: https://www.alliedacademies.org/virology-research/

Targeting viral entry: Novel inhibitors of host-pathogen interactions.

Edward Carl*

Department of Virology, Federal University of Minas Gerais, Brazil

***Correspondence to:** Edward Carl, Department of Virology, Federal University of Minas Gerais, Brazil, E-mail: edward@princeton.edu

Received: *04-Apr-2025, Manuscript No. AAVRJ-25-171341;* ***Editor assigned:*** *05-Apr-2025, PreQC No. AAVRJ-25-171342(PQ);* ***Reviewed:*** *19-Apr-2025, QC No. AAVRJ -25-171342;* ***Revised:*** *23-Apr-2025, Manuscript No. AAVRJ -23-171341(R);* ***Published:*** *30-Apr-2025, DOI:10.35841/aavrj-9.2.192*

Introduction

The entry of viruses into host cells is the first and most critical step in establishing infection. This process involves intricate interactions between viral surface proteins and host cell receptors, often exploiting cellular machinery to gain access and initiate replication. As global health continues to face threats from emerging and re-emerging viral pathogens—such as SARS-CoV-2, HIV, influenza, and Ebola—targeting viral entry has become a strategic focal point for antiviral drug development. Novel inhibitors that disrupt host-pathogen interactions offer promising avenues for broad-spectrum and resistance-resilient therapies [1].

Viral entry typically occurs through one of two main pathways: direct fusion with the host cell membrane or endocytosis followed by fusion within endosomes. The process is mediated by viral envelope proteins (e.g., spike proteins in coronaviruses, hemagglutinin in influenza) that bind to specific host receptors such as ACE2, CD4, or sialic acid residues. These interactions trigger conformational changes that facilitate membrane fusion and genome release [2].

Understanding these molecular mechanisms has enabled the identification of key targets for therapeutic intervention—either by blocking viral proteins or by modulating host receptors and co-factors. One promising strategy involves targeting host factors essential for viral entry. Unlike direct-acting antivirals, host-targeted inhibitors are less prone to resistance due to viral mutations. Examples include: Since SARS-CoV-2 uses ACE2 for entry, soluble ACE2 decoys and ACE2-blocking antibodies have been explored to prevent viral binding. This serine protease primes the spike protein for fusion. Drugs like camostat mesylate inhibit TMPRSS2 and reduce viral infectivity. Agents such as chlorpromazine and dynasore interfere with clathrin-mediated endocytosis, impeding viral uptake [3].

These inhibitors can be repurposed from existing drugs or developed as novel compounds with improved specificity and safety profiles. Targeting viral envelope proteins directly is another effective approach. Monoclonal antibodies, small molecules, and peptides can bind to viral proteins and prevent receptor engagement or fusion. Notable examples include: Used in COVID-19 treatment, antibodies like REGN-COV2 and bamlanivimab bind to the SARS-CoV-2 spike protein, blocking ACE2 interaction. Enfuvirtide, an HIV drug, binds to gp41 and prevents membrane fusion. Similar peptides are being developed for other viruses. Synthetic molecules that mimic host receptors can act as decoys, trapping viruses before they reach cells. These inhibitors often require precise structural knowledge of viral proteins, which is increasingly accessible through cryo-electron microscopy and computational modelling [4].

Given the diversity of viral pathogens, broad-spectrum inhibitors are highly desirable. These compounds target conserved mechanisms or structures shared across multiple viruses. Examples include: Lectins bind to glycosylated viral proteins, blocking entry. Griffithsin, derived from red algae, shows activity against HIV, SARS-CoV, and Ebola. Compounds like LJ001 target viral membranes without affecting host cells, offering pan-viral activity. Targeting common receptors like heparan sulfate or integrins can inhibit a range of viruses. Such inhibitors are particularly valuable in pandemic preparedness and emerging virus response. Advances in nanotechnology have enhanced the delivery and efficacy of entry

Citation: Carl E. Targeting viral entry: Novel inhibitors of host-pathogen interactions. Virol Res J. 2025;9(2):192

inhibitors. Nanoparticles can be engineered to carry antiviral agents directly to infection sites, improve bioavailability, and reduce toxicity. For instance: Used in mRNA vaccines, they can also deliver siRNA or small molecules that silence host entry factors. These decoys can bind and neutralize viruses in circulation. Ligand-functionalized nanoparticles can home in on infected tissues, increasing therapeutic precision. These innovations bridge the gap between molecular discovery and clinical application. While entry inhibitors offer potent antiviral effects, viruses can evolve escape mutations. However, host-targeted therapies exert less selective pressure on viral genomes, reducing the likelihood of resistance. Combination therapies—pairing entry inhibitors with replication blockers or immune modulators—can further mitigate resistance and enhance efficacy [5].

Conclusion

Targeting viral entry is a powerful strategy in the fight against infectious diseases. By disrupting the initial contact between virus and host, novel inhibitors can prevent infection at its earliest stage. Monitoring viral evolution through genomic surveillance is essential to adapt inhibitors and maintain therapeutic relevance. Investigated for COVID-19 treatment due to TMPRSS2 inhibition. Approved for HIV, demonstrating long-term efficacy. Advances in molecular biology, synthetic chemistry, and drug delivery are driving the development of safe, effective, and versatile entry inhibitors. As we confront evolving viral threats, these innovations will be critical in safeguarding public health and achieving therapeutic breakthroughs.

References

1. Nickol ME, Kindrachuk J. Dysregulated Host Responses Underlie 2009 Pandemic Influenza-Methicillin Resistant Staphylococcus aureus Coinfection Pathogenesis at the Alveolar-Capillary Barrier. Cells. 2020;9(11):2472.
2. Paparisto E, Hunt NR. Interferon-Induced HERC5 Inhibits Ebola Virus Particle Production and Is Antagonized by Ebola Glycoprotein. Cells. 2021;10(9):2399.
3. Courtney DG. Post-Transcriptional Regulation of Viral RNA through Epitranscriptional Modification. Cells. 2021;10(5):1129.
4. Xue L, Weilong J. Coinfection of Porcine Circovirus 2 and Pseudorabies Virus Enhances Immunosuppression and Inflammation through NF-κB, JAK/STAT, MAPK, and NLRP3 Pathwaysn. Int J Mol Sci. 2022;23(8):4469
5. Chailangkarn T, Tanwattana N. Establishment of Human-Induced Pluripotent Stem Cell-Derived Neurons-A Promising In Vitro Model for a Molecular Study of Rabies Virus and Host Interaction. Int J Mol Sci 2021;22(21):11986.

Citation: Carl E. Targeting viral entry: Novel inhibitors of host-pathogen interactions. Virol Res J. 2025;9(2):192