**Beijing Dilun Biotechnology Co., Ltd.**
Specializes in R&D and manufacturing of peptide synthesis equipment, providing comprehensive technical solutions and services.
Web: www.peptidescientific.com. Email: chengchao.wei@dilunbio.com

# Review of Research Advances on Peptides in Viral Infectious Diseases

Viral infectious diseases have long posed a serious threat to global public health. With accelerating viral mutations and the continuous emergence of novel viruses, developing new antiviral strategies has become particularly urgent. Peptides, as biologically active molecules composed of amino acids linked by peptide bonds, are gaining significant attention in antiviral drug development due to their unique advantages.

## I.Fundamental Properties and Advantages of Peptides

Peptides typically refer to short-chain molecules composed of 2–50 amino acids, occupying a size range between traditional small-molecule chemical drugs and large-molecule proteins. This structure endows peptides with a series of desirable properties: moderate molecular weight, retaining high specificity and strong affinity similar to antibodies while exhibiting tissue permeability and low immunogenicity comparable to small-molecule drugs. More importantly, peptides can be efficiently synthesized chemically and readily modified for structural optimization.

These characteristics make them an ideal scaffold for designing novel antiviral agents.

## II.Mechanism of Action of Peptide Antivirals

Peptides primarily interfere with the viral infection process through three mechanisms:

1. Directly inhibit viral entry: Many peptides are engineered to mimic key regions of viral receptor-binding domains or host cell receptors. For instance, targeting respiratory syncytial virus (RSV) and influenza viruses, researchers have developed peptides that mimic the core structure of viral fusion proteins. These peptides can preemptively bind to viruses or cells, effectively blocking the recognition and adsorption process between viruses and host cell receptors. Such peptides act like “molecular shields,” neutralizing viruses before they come into contact with cells.

2. Inhibiting viral fusion with host membranes: Enveloped viruses such as HIV, SARS-CoV-2, and herpesviruses require membrane fusion to inject their genetic material into host cells. Fusion inhibitors developed for this step—such as enfuvirtide used in HIV therapy—mimic key segments of viral fusion proteins. They competitively bind and block conformational changes, preventing membrane fusion. These peptides often employ helical designs to precisely match the target's spatial structure.

3. Modulating Host Immune Responses: Some peptides exert antiviral effects not by directly targeting viruses, but by regulating immune system functions. For example, certain peptides derived from host defense peptides can enhance macrophage phagocytic function, promote interferon secretion, or regulate inflammatory responses. This helps the body clear viruses more effectively and mitigate immune-mediated pathological damage. Such immunomodulatory peptides offer novel therapeutic approaches for treating severe conditions caused by immune overactivation.

## III. Key Research Advances and Clinical Applications

In recent years, significant progress has been made in multiple aspects of peptide antiviral research:

1.Breakthroughs in HIV Research

HIV treatment exemplifies the success of peptide therapeutics. Enfuvirtide, the first approved membrane fusion inhibitor administered via subcutaneous injection, provides a critical treatment option for patients with multidrug resistance. Building upon its mechanism of action, subsequent second-generation fusion inhibitor peptides such as Aptivus feature extended half-lives enabling weekly dosing, significantly enhancing treatment convenience.

## 2.The Quest to Combat Coronavirus

The COVID-19 pandemic has accelerated the rapid development of antiviral peptides. Based on the receptor-binding domain (RBD) or fusion core structure (HR1) of the SARS-CoV-2 spike protein, research teams have designed multiple highly active inhibitory peptides. Some candidate peptides have demonstrated broad-spectrum neutralizing capabilities against the original strain and multiple variants in animal models. These peptides can be administered via nasal spray or inhalation formulations, directly targeting respiratory mucosal surfaces to provide localized preventive protection.

## 3.New Strategies Against Influenza Viruses

Targeting the highly conserved HA2 fusion domain of influenza viruses, scientists have designed a series of stable helical-structured peptides. Unlike traditional vaccines requiring annual updates, these peptides demonstrate inhibitory activity against multiple influenza subtypes by targeting conserved regions, offering potential for developing universal influenza therapeutics.

## 4.Protection against herpes virus and other viral infections

Peptide inhibitors targeting herpes simplex virus (HSV) glycoprotein B or the gH/gL complex effectively block viral entry into cells. Additionally, a

series of peptide candidates targeting respiratory syncytial virus (RSV), dengue virus, and hepatitis B virus (HBV) have advanced into preclinical or clinical research phases.

## IV.Current Challenges and Optimization Strategies

Despite promising prospects, peptide drug development still faces challenges: susceptibility to protease degradation, limited cell membrane permeability, low oral bioavailability, and relatively high production costs.

To address these challenges, researchers are optimizing through multiple strategies:

1.Cyclization modification: Connecting the ends of linear peptides or cross-linking them via side chains to form cyclic structures significantly enhances their resistance to proteases and structural rigidity.

2.Introduction of non-natural amino acids: Substituting with D-amino acids or specially designed synthetic amino acids can effectively resist enzymatic hydrolysis and extend the half-life.

3.Lipid Modification and Conjugation: Attaching fatty acid chains or cholesterol groups can enhance peptide interaction with cell membranes, thereby improving their ability to enter cells.

4.Development of Novel Delivery Systems: Enhancing peptide delivery efficiency and targeting through methods such as nanoparticle encapsulation, transdermal patches, or inhalation formulations.

## V.Future Outlook

With the deep integration of bioinformatics, artificial intelligence, and structural biology, the development of peptide drugs is entering a new phase of rational design. Predicting peptide interactions with viral targets through machine learning, combined with high-throughput screening, will significantly accelerate the discovery of highly effective, broad-spectrum antiviral peptides.

In the future, peptide drugs may not only serve as monotherapies but also be combined with existing small-molecule drugs or antibody therapeutics to achieve synergistic effects. Furthermore, “prodrug” peptides that activate in response to viral protease environments, along with dual-functional or multifunctional peptides capable of simultaneously targeting multiple stages of the viral lifecycle, represent highly promising avenues for development.

## VI.Conclusion

Peptide drugs demonstrate irreplaceable value in antiviral therapy due to their unique mechanisms of action and design flexibility. From the

success in HIV treatment to the rapid response to the COVID-19 pandemic, peptide technology has proven its formidable potential. With ongoing breakthroughs in key technologies, these molecules are poised to provide more precise, efficient, and safe weapons for humanity to combat current and future emerging and re-emerging viral threats, becoming a crucial component in infectious disease prevention and control systems.