Review

Current progress in antiviral strategies

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The prevalence of chronic viral infectious diseases, such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), and influenza virus; the emergence and re-emergence of new viral infections, such as picornaviruses and coronaviruses; and, particularly, resistance to currently used antiviral drugs have led to increased demand for new antiviral strategies and reagents. Increased understanding of the molecular mechanisms of viral infection has provided great potential for the discovery of new antiviral agents that target viral proteins or host factors. Virus-targeting antivirals can function directly or indirectly to inhibit the biological functions of viral proteins, mostly enzymatic activities, or to block viral replication machinery. Host-targeting antivirals target the host proteins that are involved in the viral life cycle, regulating the function of the immune system or other cellular processes in host cells. Here we review key targets and considerations for the development of both antiviral strategies.

Current antiviral strategies

Viruses comprise a large group of pathogens that are responsible for causing severe infectious diseases. Over the past 30 years, antiviral agents that target viral proteins or host factors have been successfully developed. Based on their inhibitory mechanisms, antiviral reagents can be divided into two groups: (i) inhibitors that target the viruses themselves or (ii) inhibitors that target host cell factors. Virus-targeting antivirals (VTAs) can function directly (DVTAs) or indirectly (InDVTAs) to inhibit biological functions of viral proteins, mostly enzymatic activities, or they block the correct formation of the viral replication machinery (Table 1). Host-targeting antivirals (HTAs) include reagents that target the host proteins that are involved in the viral life cycle (Figure 1), regulating the function of the immune system or other cellular processes in host cells. With increased knowledge of viral protein and host factors, the scientific community has achieved great progress in mechanism-based antiviral discovery against chronic viral infectious diseases, and in understanding of the emergence of new viral diseases and of the resistance to traditional antivirals. This review will highlight recent achievements in antiviral development and discuss various strategies for preventing virus attachment and entry into the host cell, as well as strategies for preventing virus replication and transcription within the host cell.

Direct virus-targeting antivirals

Attachment inhibitors

The first step in viral invasion is the attachment to host cells via an interaction with functional receptor(s). For enveloped viruses, the viral proteins located on the outer envelope of the virion are responsible for the recognition of receptors and the attachment to host cells. HIV (a member of the Retroviridae family) is a typical enveloped virus, and its invasion is mediated by the envelope proteins gp120 and gp41, which are arranged on the viral membrane as a trimer of three trans-membrane gp41 and three noncovalently attached gp120 surface subunits [1] (Figure 2). gp120 recognizes the CD4 receptor and launches the conformational changes that expose the binding sites for the binding of a co-receptor, (i.e., CCR5 and CXCR4 [2]). Antagonists that block the interactions between HIV and its receptor and co-receptors have therefore been developed as anti-HIV therapeutics. Attempts to find specific inhibitors that block the interaction between HIV-1 and CD4 were initiated using a soluble extracellular domain of CD4 protein that retained the ability to bind gp120. Although the preliminary results revealed that either soluble CD4 protein or a CD4–immunoglobulin fusion protein showed good *in vitro* anti-HIV activity, all failed in clinical trials due to poor pharmacokinetic features (e.g., the half-life of CD4–immunoglobulin fusion protein in mice is only 2.4 h) [3–5]. Small molecule inhibitors that occupy a specific region within the CD4-binding pocket of gp120 were subsequently developed to block the gp120–CD4 interaction (Figure 2A). For example, BMS488043 [6] and BMS663068 [7] were found to significantly reduce HIV-1 proliferation and have good pharmaceutical characteristics.

Another success is influenza neuraminidase (NA) inhibitor (NAI). Influenza NA is a surface glycoprotein and functions at two steps of the viral life cycle: (i) cleaves the cell receptor sialic acid residues, which bind to influenza hemagglutinin (HA), and allows the release of the progeny virus; and (ii) cleaves the sialic acid moieties on the mucin that bathes the airway epithelial cells or co-binds the receptor with HA [8]. In line with the structure of

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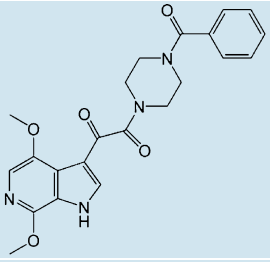
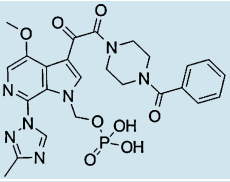
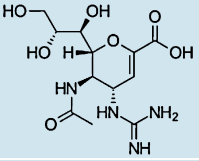
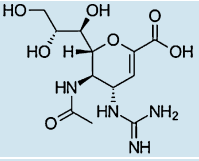
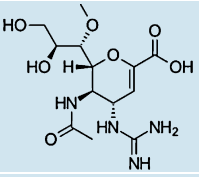
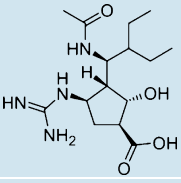
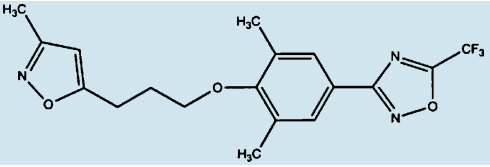
Table 1. A summary of the antivirals described in this review

Group	Subgroup	Name	Structure formula	Target and mechanism
Direct virus-targeting antivirals (DVTAs)	Attachment inhibitors	BMS488043		Block HIV-1 gp120–CD4 interaction
		BMS663068		
		ICAM-1		Block HRV–receptor interaction
		Oseltamivir		Influenza NAI
		Zanamivir		
		Laninamivir		
		Peramivir		
	Entry inhibitors	T20 peptide (Enfuvirtide)	YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF	Block the conformational changes of HIV-1 gp41
		Cp32M	VEWNEMTWMEWEREIENYTKLIYKILESSQEQ	
		Sifuvirtide	SWETWEREIENYTRQIYRILEESQEQQDRNERDLLE	
		T2635	TTWEAWDRAIAEYAARIEALIRAAQEQQEKNEAALREL	
		Pleconaril		Replace the natural pocket factor and inhibit picornaviral uncoating
		BTA798