CHAPTER 1

Overview of Antiviral Drug Discovery and Development: Viral Versus *Host Targets*

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1.1 Introduction

During recent decades, a great variety of viral and host targets have been exploited for the discovery of antiviral agents against human infectious diseases.[1] Although significant progress has been made in antiviral drug discovery, it remains a difficult task to eliminate viral infections, except for hepatitis C infections which can be cured by direct-acting antivirals.[2]

Two approaches have been widely applied to discover antiviral agents: (i) drugs targeting viral proteins that play a key role in the viral life cycle; and (ii) drugs targeting indispensable host factors, thereby indirectly inhibiting viral infections. The former approach gained its popularity based on the approval of more than 80 antiviral agents (Table 1.1), but most inhibitors are prone to drug resistance. The latter approach may lead to broad-spectrum inhibitors that interfere with cellular functions required by multiple viruses, and a low risk of drug resistance in conserved host factors.[3] Furthermore, host-targeted antivirals are often more prone to side effects compared with viral-targeted antivirals.

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Table 1.1 Summary of viral proteins targeted by approved and novel inhibitors.

Human viruses	Viral targets	Approved drugs	Novel inhibitors
Human immunodeficiency virus (HIV)	Protease	Saquinavir, ritonavir, indinavir, nelfinavir, lopinavir, atazanavir, fosamprenavir, tipranavir, darunavir	
	Reverse transcriptase	NRTIs: zidovudine, didanosine, stavudine, lamivudine, abacavir, emtricitabine, tenofovir, tenofovir alafenamide	MK-8591 (phase 2), GS-9131 (phase 2)
		NNRTIs: nevirapine, efavirenz, delavirdine[a], elsulfavirine[b], rilpivirine, etravirine, doravirine	MK-1650 (phase 2)
	Integrase	Raltegravir, elvitegravir, dolutegravir, bictegravir	Cabotegrar (phase 3), GSK3640254 (phase 2)
	gp41	Enfuvirtide, albuvirtide[b]	GSK3732394 (phase 1)
	gp120		Fostemsavir (phase 3)
Hepatitis C virus (HCV)	NS3/4A protease	Simeprevir, paritaprevir, grazoprevir, paritaprevir, glecaprevir	
	NS5A phosphoprotein	Daclatasvir, ledipasvir, ombitasvir, elbasvir, velpatasvir, pibrentasvir	
	NS5B polymerase	Sofosbuvir, dasabuvir	
Human influenza virus	RNA polymerase	Baloxavir marboxil, favipiravir[b]	Pimodivir (phase 3)
	Neuraminidase	Oseltamivir, zanamivir, peramivir, laninamivir[b]	
	Hemagglutinin	Arbidol[b]	
	Matrix protein 2	Rimantadine, amantadine[a]	
Respiratory syncytial virus (RSV)	RNA polymerase	Ribavirin	
	Fusion glycoprotein	Palivizumab	
Herpes simplex virus (HSV)	DNA polymerase UL30	Idoxuridine, brivudine, trifluridine foscarnet, acyclovir, famciclovir, valaciclovir, penciclovir	
	Envelope proteins	Docosanol[c]	
Human cytomegalovirus (HCMV)	DNA polymerase UL54	Foscarnet, ganciclovir, valganciclovir, cidofovir, fomivirsen[c]	
	Terminase UL56	Letermovir	
Varicella-zoster virus (VZV)	DNA polymerase	Acyclovir, famciclovir, valaciclovir, brivudine, vidarabine[c]	
Hepatitis B virus (HBV)	DNA polymerase	Entecavir, telbivudine, adefovir, tenofovir, tenofovir alafenamide, clevudine[b]	
Human smallpox	VP37 envelope wrapping protein	Tecovirimat	

[a]Discontinued.
[b]Elsulfavirine was approved in Russia, albuvirtide was approved in China; favipiravir and laninamivir were approved in Japan; clevudine was approved in South Korea and the Philippines; Arbidol (umifenovir) was approved in Russia and China for seasonal influenza.
[c]Docosanol may inhibit the fusion of the HSV envelope with host cell plasma membranes, but its exact mechanism of action remains unclear.

This chapter aims at providing an overview of viral and host targets in the hope of developing effective antivirals against a broad spectrum of human viruses. First, we describe popular viral targets for major viral infections: hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex virus (HSV), human cytomegalovirus (HCMV), human immunodeficiency virus (HIV), human influenza virus, respiratory syncytial virus (RSV), and varicella-zoster virus (VZV).[1] Approved and promising inhibitors targeting 20 viral proteins will be summarized. Second, we introduce 12 important host targets with special interests to reveal why their biological functions and structures are eligible for antiviral drug development. Third, the advantages and disadvantages of viral and host targets will be discussed thereafter. Information on viral and host targets will be updated on our research platform (http://www.virusface.com).

1.2 Viral Targets for Antiviral Drugs

Most antiviral compounds, especially those approved by the FDA, have been designed to target viral proteins (Table 1.1). Based on protein functions, drug targets can be arbitrarily divided into 5 classes: viral polymerases, viral proteases, viral integrases, structural proteins, and accessory proteins. For each class, we will describe viral protein functions, drug binding pockets, as well as approved and promising inhibitors. Viral protein structures are visualized in Figure 1.1.

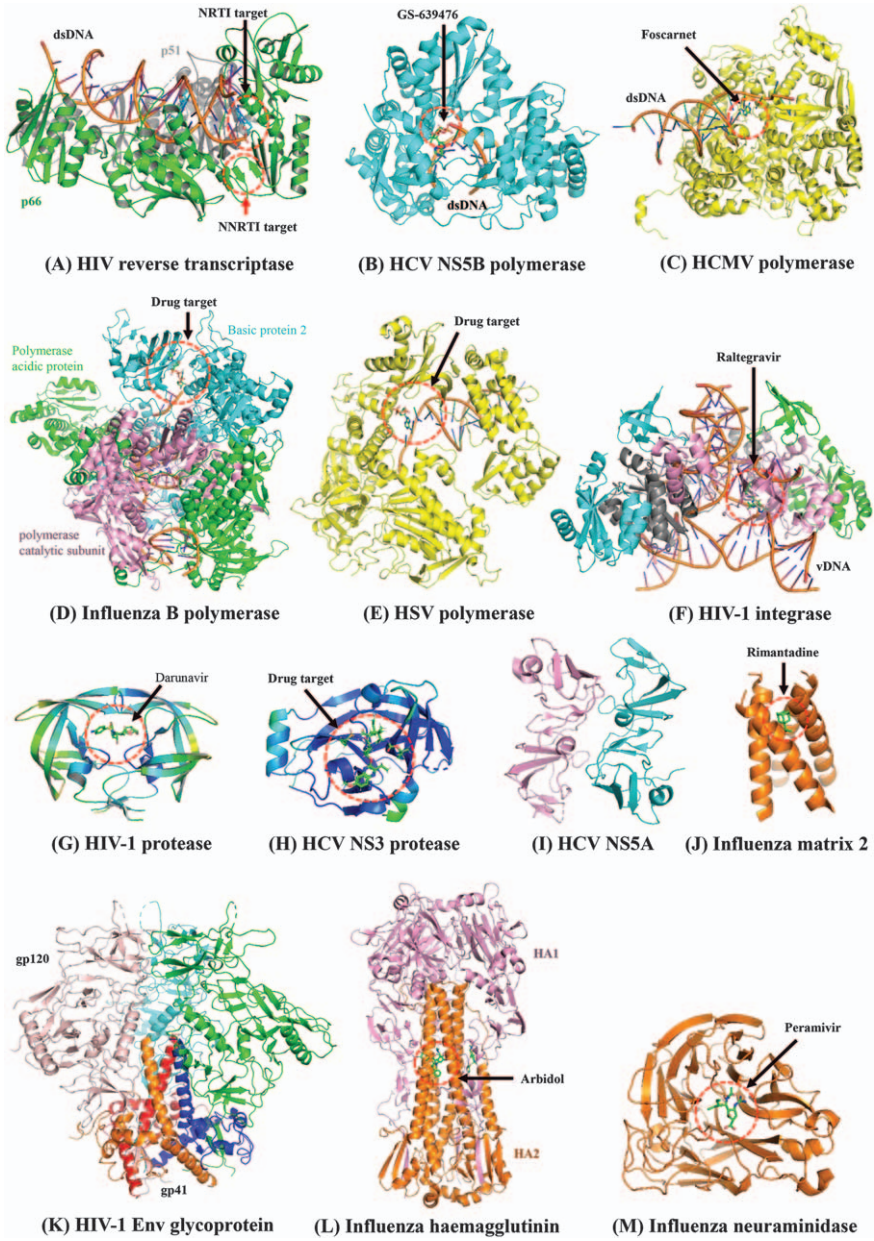
1.2.1 Viral Polymerases

Viral polymerases are the major targets of nucleos(t)ide analogs approved for the treatment of eight viral infections: HIV, HBV, HCV, HSV, influenza, RSV, VZV, and HCMV. Moreover, Ebola polymerase is targeted by promising nucleoside inhibitors such as remdesivir (GS-5734) (see our recent review ref. 4). This subsection will focus on seven viral polymerases targeted by FDA-approved inhibitors.

1.2.1.1 HIV Reverse Transcriptase

HIV reverse transcriptase is an RNA-dependent DNA polymerase that produces the complementary DNA from an RNA template – a key process called reverse transcription in the HIV life cycle.[5] The asymmetric heterodimer of HIV reverse transcriptase is constructed by two subunits: p66 and p51 (Figure 1.1A). In the palm domain of the p66 subunit, an active site with three catalytic carboxylates (D110, D185, D186) is responsible for the polymerase catalytic function which produces the double-stranded DNA genome from the single-stranded viral RNA genome. Due to its significance, the polymerase active site (Figure 1.1A) is recognized as a key target to develop nucleoside reverse transcriptase inhibitors (NRTIs). Another important target is the allosteric binding site of non-nucleoside reverse transcriptase inhibitors (NNRTIs), which is a hydrophobic pocket approximately 10 to 15 Å beneath the polymerase active site. As of August 2019, eight NRTIs and seven

NNRTIs have been approved (Table 1.1). Many novel NNRTIs (*e.g.* VM1500A, Cmpd I,[6] compounds K-5a2 and 25a[7]) have been proposed, but they still need to undergo clinical testing. Moreover, new NRTIs such as censavudine,[8] GS-9131 (NCT03472326), and MK-8591 (NCT03272347) have been evaluated in phase 2 trials.



1.2.1.2 HBV Polymerase

HBV polymerase is a viral enzyme that performs the activities of both RNA-dependent and DNA-dependent DNA polymerase. HBV polymerase is composed of four functional domains: reverse transcriptase, terminal protein, spacer domain, and RNase H domain.[9] As the hotspot target of HBV inhibitors, the active site of reverse transcriptase in the HBV polymerase is critical for protein priming and viral DNA synthesis.[10] As of August 2019, there are five FDA-approved inhibitors targeting the active site of HBV polymerase, and one polymerase compound clevudine was approved in South Korea and the Philippines (Table 1.1). Most HBV nucleos(t)ide inhibitors such as lamivudine and adefovir can target the dNTP-binding pocket and block the DNA chain elongation, because they lack the 3′-hydroxyl group required for nucleotide addition. As a guanosine analog, entecavir also inhibits the priming initiation before polymerization due to its competition with the deoxy-guanosine triphosphate (dGTP) – a nucleotide precursor used for DNA synthesis.

1.2.1.3 HCV NS5B Polymerase

HCV NS5B polymerase is an RNA-dependent RNA polymerase that plays an essential role in HCV RNA synthesis and genome replication. As shown in Figure 1.1B, the 3D structure of HCV NS5B polymerase is characterized by thumb, finger, and palm domains. In the palm domain, the catalytic site of NS5B uses HCV positive-strand RNA as a template for the polymerization of ribonucleoside triphosphates. This catalytic site is targeted by nucleotide inhibitors (*e.g.* sofosbuvir), which act as a competitor of nucleotide triphosphate to block HCV RNA synthesis.[2] At least four allosteric pockets have been targeted by non-nucleoside NS5B inhibitors: (i) thumb I site targeted by beclabuvir,[11] (ii) thumb II site targeted by filibuvir,[12] (iii) palm I site targeted by dasabuvir,[13] and (iv) palm II site targeted by GSK5852.[14] Although many NS5B inhibitors have been synthesized, as of August 2019, dasabuvir (ABT-333) remains the only nonnucleoside NS5B inhibitor approved by the FDA.

Figure 1.1 Viral proteins targeted by antiviral agents. (A) HIV-1 reverse transcriptase in complex with dsDNA and the NRTI emtricitabine triphosphate (PDB code: 6OTZ). (B) HCV NS5B polymerase targeted by GS-639476 (5UJ2). (C) HCMV DNA polymerase targeted by foscarnet (3KD5). (D) Influenza B virus polymerase in complex with viral RNA (6QCT). (E) HSV polymerase (2GV9, 4M3R). (F) HIV-1 integrase tetramer targeted by raltegravir (5U1C, 3L2V). (G) HIV-1 protease dimer targeted by darunavir (3OY4). (H) HCV NS3 protease targeted by the MK-5172 analog (5EQQ). (I) HCV NS5A dimer structure (4CL1). (J) Influenza A matrix 2 protein targeted by rimantadine (6BKL). (K) HIV-1 Env glycoprotein in the trimeric form of gp120 and gp41 (6OT1). (L) Influenza A virus hemagglutinin targeted by Arbidol (5T6N). (M) Influenza A neuraminidase targeted by peramivir (4MWV). Drug binding pockets are indicated by red circles. Protein structures were visualized using the software PyMOL V2.1 (http://www.pymol.org/).

1.2.1.4 HCMV Polymerase

HCMV polymerase, encoded by the UL54 gene (length: 1242 amino acids), belongs to the B family of DNA polymerases. In order to perform DNA polymerization, HCMV DNA polymerase contains five important domains: (i) a palm domain possesses a catalytic site of viral polymerase; (ii) a thumb domain takes part in the DNA duplex binding; (iii) a finger domain acts as the nucleotide substrate binding site; (iv) 3′–5′ exonuclease removes mismatched nucleotides from the primer DNA strand; and (v) a ribonuclease (RNase) H domain degrades the RNA primers.[15]

All approved inhibitors (ganciclovir, valganciclovir, foscarnet, cidofovir) share the same drug target at the catalytic site within the palm domain of HCMV polymerase (Figure 1.1C). Ganciclovir and its prodrug valganciclovir are commonly used as first-line agents for HCMV prevention and treatment, while cidofovir and foscarnet injections are second-line agents due to their toxicities and lack of oral formulations. Novel inhibitors (*e.g.* filociclovir, CX-5461) are currently under development. For instance, in a phase 1b study, the methylenecyclopropane nucleoside inhibitor filociclovir was well tolerated in 18 healthy volunteers.[16] CX-5461 is an investigational inhibitor that binds to the G-quadruplex DNA structures, thereby inhibiting the DNA transcription exerted by HCMV polymerase.[17]

1.2.1.5 Influenza Polymerase

Influenza polymerase is a viral RNA-dependent RNA polymerase that conducts viral transcription and replication using one single-stranded negative-sense genomic RNA.[18] Influenza polymerase in the form of the heterotrimeric complex is composed of three subunits: polymerase basic protein 1 (PB1), polymerase basic protein 2 (PB2), and polymerase acidic protein (PA) (Figure 1.1D). Influenza polymerase hijacks the host mRNA transcription system to synthesize viral RNA.[19] First, the cap-binding pocket of the PB2 subunit hijacks the 5′-capped end of cellular pre-mRNA whose first 10 to 13 residues are subsequently cleaved by the PA endonuclease. Next, the snatched 5′-capped primer is used to transcribe the viral RNA genome at the catalytic site of the PB1 subunit.[20]

Due to their functional importance, the PA endonuclease and PB1 catalytic site are popular antiviral targets. Baloxavir marboxil was the first PA endonuclease inhibitor approved by the FDA in October 2018 to treat influenza A and B infections. Baloxavir is the active form of baloxavir marboxil that inhibits the activity of cap-dependent PA endonuclease.[21] Crystallization analyses suggest that baloxavir binds to the active site of PA endonuclease *via* van der Waals interactions .[22] As a purine nucleotide analog approved in Japan, favipiravir (T-705, Avigan) in its active form (favipiravir-RTP) can inhibit viral replication and transcription.[23] Pimodivir (VX-787, JNJ-3872) is an investigational PB2 inhibitor currently evaluated in phase 3 trials (NCT03381196, NCT03376321). In a phase 2 study, pimodivir 600 mg with or without oseltamivir offered promising virological responses against influenza A infections.[24]

1.2.1.6 HSV Polymerase

HSV-1 DNA polymerase, encoded by the UL30 gene, takes part in the proofreading and polymerization activities during viral DNA replication.[25] Its structure is composed of a pre-NH_2-terminal domain, an N-terminus, finger/palm/thumb domains, and a 3′–5′ exonuclease domain. The finger and palm domains hold a conserved interface that is crucial for the catalytic site of HSV-1 DNA polymerase (Figure 1.2). This catalytic site is the popular target of eight FDA-approved inhibitors (Table 1.1), which share similar mechanisms of drug action. For instance, after its phosphorylation by viral thymidine kinase and cellular kinases, acyclovir triphosphate can inhibit the DNA elongation exerted by HSV-1 DNA polymerase. Many novel inhibitors (*e.g.* psoromic acid,[26] alpha-carboxynucleoside phosphonates[27]) have been developed to target HSV DNA polymerase, but their clinical evaluations are still needed. Of interest, tenofovir represents a good example of repurposing the FDA-approved inhibitors for HSV treatment. In addition to its anti-HIV activity, the active tenofovir metabolite targets the DNA polymerase of HSV-1 and HSV-2, thereby inhibiting the viral DNA replication.[28] Nevertheless, resistant mutations selected by the acyclovir and/or foscarnet could induce cross-resistance to tenofovir.[29]

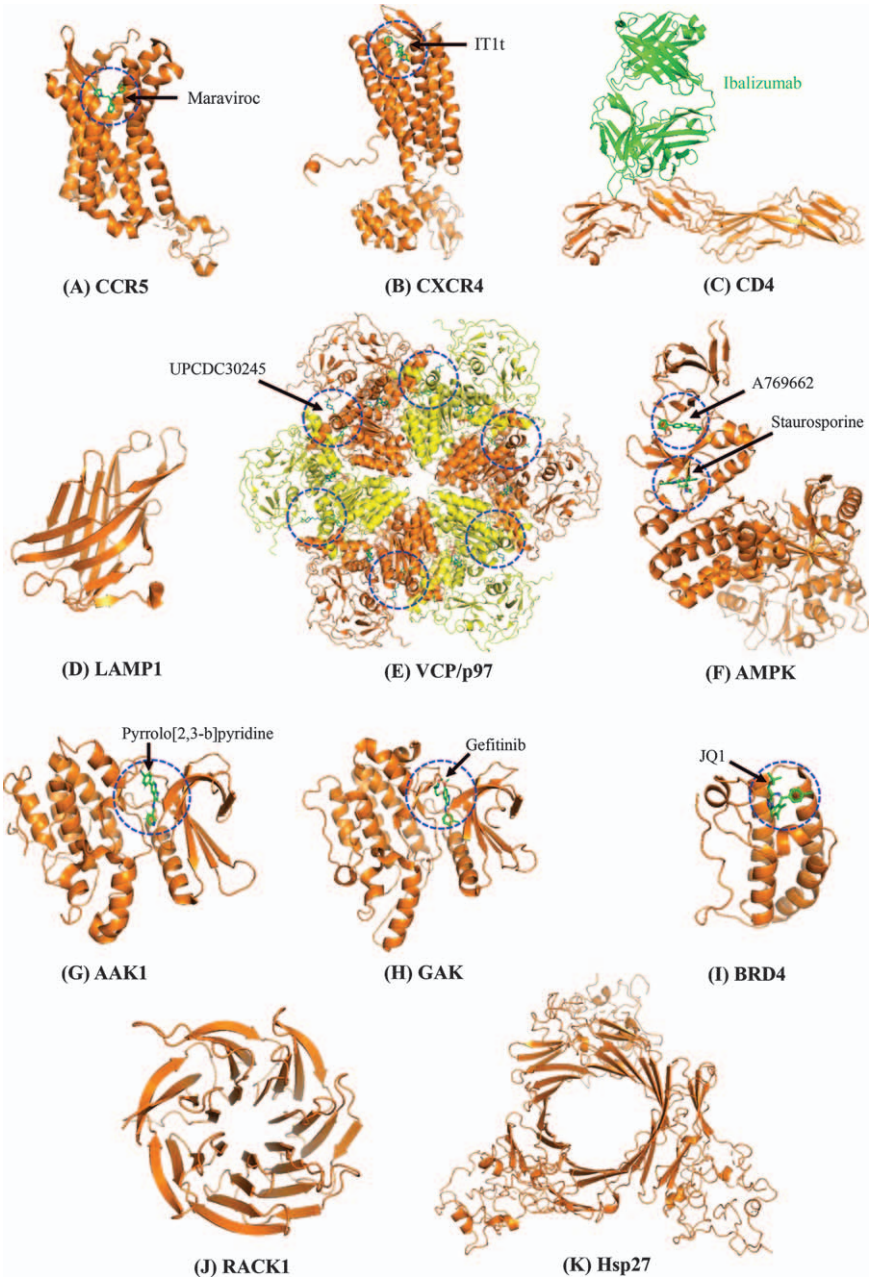
1.2.1.7 RSV Polymerase

RSV polymerase is an RNA-dependent RNA polymerase for RSV replication and transcription.[30] The 3D structure of RSV polymerase is formed by a large protein and a phosphoprotein in complex with host cofactors. The large protein performs all enzymatic activities such as RNA synthesis, mRNA capping, and mRNA polyadenylation, while the phosphoprotein subunit acts as an essential cofactor.[31] Due to its enzymatic activities, the large protein remains the key drug target. Nucleoside inhibitors can target the active site of the large protein, while allosteric inhibitors could bind to other regions of RSV polymerase. Although its mechanisms of action remain unclear, ribavirin was the only approved nucleoside analog to treat RSV infections. Nevertheless, the use of ribavirin in RSV treatment is widely abandoned because of its limited efficacy and strong adverse events (*e.g.* hemolytic anemia). Other promising analogs such as PC786 and lumicitabine (ALS-008176, JNJ-64041575) are still under evaluation. Note that PC786 is a nonnucleoside inhibitor that rapidly reduces RSV viral loads in the human airway epithelium.[32]

1.2.1.8 VZV Polymerase

VZV polymerase is a DNA polymerase which is composed of an N-terminal domain, finger, palm, and thumb domains, and an exonuclease domain. During the polymerization of VZV genomes, the thumb domain holds the primer–template complex. Subsequently, the palm plus finger domains incorporate the incoming nucleoside triphosphates, while the exonuclease domain is responsible for the proofreading activity.[25] Due to its functional importance, the catalytic site of VZV polymerase is the major target of

approved VZV inhibitors (acyclovir, famciclovir, valaciclovir, brivudine, and the discontinued vidarabine) to prevent or cure VZV-associated diseases.[33] For instance, after its phosphorylation by viral thymidine kinase, acyclovir targets the viral DNA polymerase and inhibits the viral genome replication.



Investigational compounds (*e.g.* FV-100[34] and valomaciclovir) are currently being evaluated for the treatment of herpes zoster-associated diseases. Foscarnet is repurposed to inhibit VZV polymerase,[35] but it has not been approved for VZV treatment.

1.2.2 Viral Integrase

1.2.2.1 HIV Integrase

HIV integrase is essential for integrating the full-length linear HIV DNA genome into host chromatin.[36] The catalytic activities of 3′-processing and strand transfer are conducted by HIV integrase. The viral 3′-processing action removes the last two nucleotides at the 3′-ends of viral DNA strands so that a pre-integration complex with HIV integrases plus other cofactors can stabilize with the newly transcribed viral DNA. The strand transfer reaction catalyzes the integration of the viral DNA genome into the host chromatin.[36] As shown in Figure 1.1F, the catalytic site of HIV integrase with the conserved catalytic triad Asp64–Asp116–Glu152 is targeted by the drug class of integrase strand transfer inhibitors (INSTIs), which displace the 3′ end of the viral DNA from the active site and chelate the divalent cations (Mg^{2+} or Mn^{2+}) required for the strand transfer.[37] Four integrase inhibitors (raltegravir, elvitegravir, dolutegravir, and bictegravir) have been approved by the FDA, while other promising candidates (*e.g.* cabotegravir, GSK 3640254) are being evaluated in ongoing trials. For instance, cabotegravir plus rilpivirine at 4 week or 8 week intervals maintained viral suppression in a phase 2b trial.[38] In clinical practice, integrase inhibitors with a high genetic barrier to resistance are key elements of highly active antiretroviral therapy.

1.2.3 Viral Proteases

1.2.3.1 HIV Protease

HIV protease is a homodimeric aspartyl protease (length: 99 amino acids) that cleaves Gag and Gag-Pol polyproteins at 9 specific cleavage sites in order to produce three viral enzymes (protease, reverse transcriptase, and integrase) and four structural proteins (matrix, capsid, nucleocapsid, and p6).[39]

Figure 1.2 Host proteins targeted by antiviral agents. (A) CCR5 chemokine receptor targeted by maraviroc (PDB code: 4MBS). (B) CXCR4 chemokine receptor targeted by its inhibitor IT1t (3ODU). (C) CD4 targeted by its antibody ibalizumab (3O2D, 6MET). (D) LAMP1 protein structure (5GV0). (E) VCP/p97 hexamer targeted by its inhibitor UPCDC30245 (5FTJ). (F) AMPK targeted by its activators staurosporine and A769662 (4QFR). (G) AAK1 targeted by its inhibitor pyrrolo[2,3-*b*]pyridine (5L4Q). (H) GAK targeted by its inhibitor gefitinib (5Y7Z). (I) BRD4 targeted by its inhibitor JQ1 (3MXF). (J) RACK1 formed as a sevenfold β-propeller (4AOW). (K) Hsp 27 hexamer (6DV5). Drug binding pockets are indicated by blue circles. Protein structures were visualized using the software PyMOL V2.1 (http://www.pymol.org/).

As an essential drug target, the catalytic site of HIV protease with the conserved sequence Asp25–Thr26–Gly27 is located in a central cavity between two protease monomers (Figure 1.1G). As of August 2019, nine protease inhibitors have been approved: saquinavir, ritonavir, indinavir, nelfinavir, lopinavir, atazanavir, fosamprenavir, tipranavir, and darunavir. As a novel HIV-1 protease inhibitor, GRL-142 shows strong antiviral activity against a variety of HIV-1 resistant strains (IC_{50}: attomolar to picomolar concentrations).[40]

1.2.3.2 HCV NS3/4A Protease

HCV NS3 protease is a serine protease in complex with its cofactor NS4A – a nonstructural protein adjacent to NS3 in the viral genome. The non-covalent formation of the HCV NS3/4A complex is essential for the proteolytic cleavage at four junction sites in the polyprotein to produce nonstructural proteins.[41] HCV NS3 protein contains N-terminal serine protease and C-terminal RNA helicase, while its cofactor NS4A enhances protease activities and anchors the NS3/4A complex to intracellular membranes.[42] The catalytic site of HCV NS3 protease with a conserved catalytic triad His57–Asp81–Ser139 is targeted by HCV protease inhibitors (Figure 1.1H), which block NS3-dependent polyprotein cleavages and inhibit RNA synthesis.[41] With similar mechanisms of action, five HCV protease inhibitors have been approved by the FDA, including simeprevir, paritaprevir, grazoprevir, paritaprevir, and glecaprevir (Table 1.1). Danoprevir in a combination therapy was approved in China to treat HCV genotype 1b infections.[43] Novel NS3/4A inhibitors (*e.g.* seraprevir) are currently under development. Seraprevir is now evaluated in a phase 3 trial (NCT04001608).

1.2.4 Structural Proteins

This section will focus on structural proteins of HIV, influenza, RSV, and HSV, which have been targeted by approved antiviral agents, while information of other viral structural proteins such as HIV capsid[44] can be found elsewhere.

1.2.4.1 HIV gp120 and gp41

HIV envelope glycoproteins, gp120 and gp41, are critical for viral entry. HIV Env spikes on the viral surface have a trimeric structure formed by two noncovalently bound subunits: the receptor-binding protein gp120 and the transmembrane protein gp41.[45] The viral entry begins with the recognition of gp120 by the primary receptor CD4 and a co-receptor (*e.g.* CCR5 or CXCR4) on host cells such as CD4+ T cells, macrophages, and dendritic cells. Subsequently, conformation changes of the gp120–gp41 trimer trigger the fusion of HIV particles to the host membrane, allowing the release of the HIV genome into the cytoplasm. Due to its important role during viral entry,

HIV Env protein is a key target of antiviral agents and vaccines. In order to block the viral entry, HIV-neutralizing antibodies and HIV-derived peptide mimics have been developed to target gp120 or gp41 (Figure 1.1K).

As the only HIV-derived peptide approved by the FDA, T20 (enfuvirtide) with a length of 36 amino acids is derived from the C-terminal heptad repeat (CHR) (positions: 638–673) of HIV-1 gp41. T20 is a mimic peptide of the CHR structure and competes with the binding of CHR to the N-terminal heptad repeat of gp41, thereby blocking the trimeric formation of helical hairpins in the viral membrane fusion. Albuvirtide (FB006) is another CHR-derived peptide inhibitor that was approved in China in 2018. Under evaluation in a phase 2 trial (NCT03719664), 3BNC117 is a novel neutralizing antibody isolated from B cells of HIV-1-infected individuals that blocks the interaction of the CD4 receptor with gp120.[46] Other candidates (*e.g.* fostemsavir, VRC01, 2G12, 4E10, 2F5) are being clinically evaluated.[47]

1.2.4.2 Influenza Hemagglutinin and Neuraminidase

Hemagglutinin and neuraminidase are major surface glycoproteins of influenza particles that interact with sialic acids on glycoproteins or glycolipids of host-cell membranes. However, two proteins exert opposite functions. To initiate viral entry, influenza hemagglutinin (Figure 1.1L) binds to sialic acids expressed by the cellular receptors on the extracellular membranes of host cells, thereby triggering endocytosis or micropinocytosis.[48] To complete the viral budding, influenza neuraminidase (Figure 1.1M) cleaves sialic acids from both viral and host glycoproteins, therefore releasing influenza progenies from influenza-infected cells.[49]

Neuraminidase inhibitors are competitive analogs of sialic acids that target the conserved active site of neuraminidase, thereby inhibiting its enzymatic activities and preventing viral release.[49] Arbidol (umifenovir), shown in Figure 1.1L, was the only hemagglutinin inhibitor approved in Russia and China, and this indole derivative could effectively inhibit the hemagglutinin-mediated membrane fusion.[50] Four neuraminidase inhibitors have been approved to treat influenza A and B infections, including oral oseltamivir, inhaled zanamivir, intravenous peramivir, and inhaled laninamivir. Oral oseltamivir is recommended as a first-line therapy unless drug-resistant mutations are detected. Many investigational compounds have been developed to inhibit hemagglutinin and neuraminidase, but few have entered phase 2 or 3 clinical trials.[51]

1.2.4.3 RSV Fusion Glycoprotein

RSV fusion (F) glycoproteins on the viral surface facilitate the viral attachment to host cells and actively mediate the fusion between the viral and host membranes during viral entry.[52] RSV fusion protein is a class I glycoprotein whose precursor is activated by the proteolytic cleavage which produces a compact post-fusion trimer of fusion protein through a series of

conformation rearrangements.[53] Due to its important role in viral budding and fusion, RSV fusion glycoprotein is a key drug target in developing RSV entry inhibitors.[54] As the only approved RSV fusion inhibitor, palivizumab is a humanized monoclonal antibody that targets RSV fusion glycoprotein and blocks the viral fusion.[55] Nevertheless, the use of palivizumab antibody is limited to passive immunoprophylaxis of high-risk infants due to its high cost and modest effectiveness at reducing hospitalization rate (approximately 60%).[54] Novel RSV fusion inhibitors such as presatovir (GS-5806) and JNJ-53718678 have been evaluated in phase 2 trials.[54]

1.2.4.4 Smallpox VP37 Envelope Wrapping Protein

Smallpox VP37 envelope wrapping protein, encoded by the gene F13L, interacts with cellular proteins (*e.g.* Rab9 GTPase, TIP47) in the trans-Golgi membranes to wrap intracellular viral particles into a triple-wrapped form.[56,57] Subsequently, the triple-wrapped virus fuses with cellular membranes for its release into the extracellular space. The absence of VP37 blocks the transport of viral particles to extracellular membranes.[56] Approved by the FDA in July 2018, tecovirimat (ST-246) targets the viral VP37 which plays an important role in the cell-to-cell transmission of the smallpox virus. According to the FDA label, tecovirimat can inhibit the interaction of VP37 with cellular Rab9 GTPase and TIP47 (a key effector for Rab9 localization), therefore preventing the viral budding of enveloped virions. Since its eradication declared in 1980, smallpox remains a potential threat while tecovirimat offers the first approved antiviral drug mainly based on the evidence of animal models.[58] No other VP37 inhibitor is currently under development.

1.2.5 Accessory Proteins

1.2.5.1 HCV NS5A Phosphoprotein

HCV NS5A is a monotopic membrane-associated RNA binding phosphoprotein without enzymatic functions. The exact nature of NS5A remains unclear, but it can interact with NS5B for HCV RNA replication, trigger the formation of nucleocapsids, and interact with numerous cellular factors (*e.g.* apolipoprotein E) to regulate HCV replication and assembly.[59] Functional domains of NS5A (Figure 1.1I) include a short N-terminal amphipathic helix for membrane anchoring and three distinct domains: (i) domain I forms a claw-like homodimeric structure, and (ii) domain II and III are characterized by intrinsically disordered structures.[60] Domain I is the major drug target of NS5A inhibitors which may reduce the binding affinity of HBV RNA to NS5A and alter NS5A multimerization resulting in its impaired interaction with lipid droplets.[61] As of August 2019, six NS5A inhibitors have been approved by the FDA, including daclatasvir, ledipasvir, ombitasvir, elbasvir, velpatasvir, and pibrentasvir. Moreover, novel NS5A inhibitors such as ravidasvir (NCT02961426) are now under evaluation. Ravidasvir plus sofosbuvir showed high response rates in a cohort of 300 patients infected with HCV genotype 4.[62]

1.2.5.2 Influenza Matrix Protein 2

Influenza matrix protein 2 (M2) is an integral membrane protein with multiple functions during viral entry, assembly, and budding. During viral entry, the proton channel activity of M2 integrated in the viral particles drives the acidification of the virion interior, subsequently pumping the viral ribonucleoprotein from the viral matrix protein M1 into host cells.[63] As shown in Figure 1.1J, the pore-binding site of the homotetrameric M2 channel is targeted by rimantadine and amantadine – two approved compounds for treating influenza virus A.[64] Rimantadine and amantadine have poor tolerability and their clinical efficacy is limited due to the naturally occurring drug-resistant mutations (*e.g.* L26F, V27A, S31N) in influenza M2 protein.[64] Both inhibitors are no longer recommended for clinical use, while no M2 inhibitor is listed in the current pipelines of major pharmaceutical companies.

1.2.5.3 HCMV Terminase

HCMV terminase is a heterotrimer with three subunits: ATPase pUL56, nuclease pUL89, and the third component pUL51. After its maturation in the cytoplasm, HCMV terminase is translocated into the nucleus using the nuclear localization signal on pUL56. In the nucleus, HCMV terminase binds to head-to-tail linked HCMV genomes, so-called concatemers, and delivers these large concatemers to viral procapsids *via* the interaction between the pUL56 C-terminus and the portal protein pUL104.[65] HCMV concatemers are inserted into preformed capsids and subsequently cleaved into functional unit-length genomes for viral DNA packaging.[66] In 2017, letermovir was the first terminase inhibitor approved by the FDA for prophylaxis in HCMV-seropositive adults who have received a hematopoietic stem-cell transplant. Letermovir is a 3,4-dihydro-quinazoline-4-yl-acetic acid derivative that specifically targets the pUL56 subunit with potent antiviral activity.[67] Moreover, letermovir is not only active against viral strains resistant to HCVM polymerase inhibitors (*e.g.* ganciclovir, valganciclovir), but also shows a good safety profile because its target, the terminase complex, has no counterpart in mammalian cells.[67] No other terminase inhibitor has entered advanced clinical trials, but maribavir, a novel inhibitor against the viral pUL97 kinase, is now evaluated in two phase 3 trials (NCT02927067 and NCT02931539).

1.3 Host Targets for Antiviral Drugs

Antiviral agents have been designed to target many host proteins (Table 1.2), which can be arbitrarily divided into 4 classes: host chemokine receptors (*e.g.* CCR5), host glycoproteins (*e.g.* CD4), host kinases (*e.g.* AMPK), and other host proteins (*e.g.* Hsp27). For each class, popular host targets are described with the focus of protein functions as well as approved and novel antiviral agents. Host proteins are visualized in Figure 1.2.

1.3.1 Host Chemokine Receptors

1.3.1.1 CCR5 and CXCR4

C–C chemokine receptor type 5 (CCR5) from the beta chemokine receptor family is expressed as an integral membrane protein on the surface of various immune cells such as CD4+ T cells, dendritic cells, macrophages, monocytes, and microglia.[68] As shown in Figure 1.2A, the protein structure of CCR5 is composed of seven hydrophobic transmembrane domains with an extracellular N-terminus for gp120 binding and a cytoplasmic C-terminus for receptor trafficking, desensitization, and ligand-dependent signaling.[69,70] HIV gp120 on the viral surface binds to the chemokine receptor CCR5 or CXCR4, thereby triggering viral entry. Based on the structure of the CD4–gp120–CCR5 complex, the N-terminus of CCR5 binds to the bridging sheet of gp120, while the V3 loop of gp120 targets the chemokine recognition site 2 of CCR5.[70] CCR5 and CXCR4 share similar protein structures (Figure 1.2A and B), and both interact with the V3 loop of gp120.[70,71]

Many CCR5 antagonists have been designed to target the chemokine recognition site 2 of CCR5, thereby competing with gp120 to prevent the gp120–CCR5 interaction. As the first CCR5 antagonist, maraviroc was approved by the FDA in August 2007. Maraviroc and other CCR5 inhibitors (*e.g.* leronlimab, GRL-117C[72]) only prevent the CCR5-mediated entry, whereas HIV can develop resistance by switching viral tropism from CCR5 (R5-tropism) to CXCR4 (X4-tropism). For this reason, it is important to develop dual antagonists that inhibit both CCR5 and CXCR4. Currently, many compounds (*e.g.* GUT-70, NF297, diterpene derivatives) are under development.[73]

1.3.2 Host Glycoproteins

1.3.2.1 CD4

Cluster of differentiation 4 (CD4), a member of the immunoglobulin supergene family, is a membrane glycoprotein highly expressed on the surface of immune cells (*e.g.* T-helper cells, dendritic cells, macrophages). CD4 mainly acts as a co-receptor of T-cell receptors to mediate the communication between T-cell receptors and antigen-presenting cells. CD4 has four immunoglobin domains (D1 to D4) exposed on the extracellular surface of host cells, and the extracellular domain D1 is the binding target of HIV gp120.[70] HIV viral entry is initiated by the gp120–CD4 interactions. For this reason, CD4 is a key drug target when developing HIV entry inhibitors (Figure 1.2C). As the first CD4 inhibitor approved by the FDA, ibalizumab shows broad-spectrum activity against HIV-1 resistant strains. Moreover, ibalizumab is a non-immunosuppressive, humanized monoclonal antibody that binds to CD4, thereby competing with HIV-1 gp120 to block viral entry.[74] Note that ibalizumab is administered intravenously every 14 days and can be used along with other HIV drugs.[75] Fostemsavir in a phase 3 trial (NCT02362503) is a novel inhibitor that targets HIV-1 gp120 and blocks the gp120–CD4 interaction.[76]

Table 1.2 Summary of host proteins targeted by approved and novel antivirals.

Host proteins	Human virus	Antivirals[b]	Mechanisms of drug action	Ref.
CCR5	HIV-1	Maraviroc[a]	Maraviroc blocks the gp120–CCR5 interaction.	131
CXCR4	HIV-1	NF279	NF279 inhibits both CXCR5 and CCR5.	132
CD4	HIV-1	Ibalizumab[a]	Ibalizumab blocks the binding of gp120 to CCR5 and CXCR4.	74
NTCP	HBV	Myrcludex B	Myrcludex B blocks the binding of HBV preS1 to NTCP.	77
LAMP1	Lassa	Candidate 3.3	Candidate 3.3 blocks the binding of viral glycoproteins to LAMP1.	86
VCP/97	Rift Valley fever virus	Sorafenib	Sorafenib inhibits VCP and impedes the viral egress.	96
	HCMV, influenza	NMS-873	NMS-873 targets VCP and inhibits viral replication.	89, 94
AMPK	Zika, dengue, West Nile virus	PF-06409577	PF-06409577 activates AMPK to reduce viral infections of flaviviruses.	99
	KSHV	Metformin, AICAR	Two AMPK agonists inhibit the expression of viral lytic genes.	98
AAK1, GAK	Dengue, Ebola	Sunitinib, erlotinib	Both inhibit AAK1- and GAK-regulated viral trafficking.	101
Hsp27	Enterovirus 71	TDP	TDP protects against cytopathic effects and inhibits Enterovirus 71.	133
BRD4	HPV-16	I-BET762	I-BET762 blocks the binding of viral E2 protein to BRD4.	111
	Epstein–Barr virus	JQ1	JQ1 reduces BRD4 recruitment to prevent EBV gene expression.	108
	HIV-1	ZL0580	ZL0580 target BRD4 and suppresses HIV-1 transcription.	109
RACK1	HSV-1	SD-29, SD-29-14	Both target the phosphorylation pocket of RACK1 and inhibit viral gene expression.	113

[a]Antiviral agents were approved by the FDA.
[b]Only a few leading compounds are listed.

1.3.2.2 NTCP

Sodium taurocholate co-transporting polypeptide (NTCP), encoded by the *SLC10A1* gene, is a transmembrane glycoprotein that mediates the transport of liver-specific bile acids.[77] As a cellular receptor for primate hepadnaviruses, NTCP is highly expressed in human hepatocytes and interacts with

the preS1 protein of HBV and HDV for viral entry.[78] In addition to human hepatocytes, NTCP is also observed as a key host factor to regulate HBV infections in macaques and pigs.[79] Since NTCP is an essential receptor of HBV and HDV, novel NTCP compounds (*e.g.* myrcludex B) have been developed to inhibit HBV or HDV infections.[77] A recent study proposed that small macrocyclic peptides actively inhibited many HBV strains without any interference of the NTCP-mediated bile acid uptake.[80] As a peptide inhibitor, subcutaneous myrcludex B effectively inhibits HBV infections only with a marginal impairment of NTCP transporter activity.[77] Myrcludex B is currently being evaluated to treat HBV in a phase 2b trial (NCT02888106) and HDV in phase 2b/3 trials (NCT03852433, NCT03852719).

1.3.2.3 LAMP1

Lysosomal-associated membrane protein 1 (LAMP1) is a glycoprotein expressed primarily across lysosomal membranes to maintain lysosome integrity, but a basal level of LAMP1 (Figure 1.2A) is also expressed on plasma membranes. LAMP1 takes part in the life cycle of many viruses such as Lassa virus,[81] Kaposi's sarcoma-associated herpesvirus,[82] and human papillomavirus.[83] For instance, LAMP1 on plasma membranes serves as an indispensable factor of Lassa glycoproteins. In order to trigger the endocytic pathway, Lassa virus fusion requires a pH-dependent switch from the alpha subunit of dystroglycan to LAMP1, because LAMP1 promotes the viral fusion in less acidic endosomal compartments.[84] In this process, the glycoprotein subunit 1 of Lassa virus targets one of the 11 N-linked glycosylated residues in LAMP1.[85] A recent study identified a small compound adamantyl diphenyl piperazine 3.3, so-called candidate 3.3, that could effectively target LAMP1, thereby inhibiting the binding of Lassa glycoproteins to LAMP1 in a cholesterol-dependent manner.[86]

1.3.3 Host Kinases

1.3.3.1 VCP/p97

Valosin-containing protein (VCP or p97) is a type II AAA (ATPase-associated with various activities) ATPase. VCP participates in many cellular pathways such as vesicular trafficking, proteasomal degradation, and membrane fusion.[87,88] In addition, VCP plays important roles in the life cycle of many viruses such as HCMV, VSV, influenza, coronavirus, Sindbis virus, Coxsackievirus, enterovirus 71, and West Nile virus.[88–91] As illustrated in Figure 1.2E, many VCP inhibitors (*e.g.* UPCDC30245,[92] DBeQ,[93] NMS-873[94]) have been developed. For instance, VCP suppresses antiviral responses of IFN-β in an ATPase-dependent manner, while the IFN-β production increases in VSV-infected mice treated with DBeQ or NMS-873, two investigational inhibitors that block the ATPase activity of VCP.[93] VCP is indispensable for human coronavirus infections, while VCP loss inhibits the degradation of viral N protein in the early stage of coronavirus infections.[95] A novel VCP inhibitor NMS-873 not only inhibits influenza replication and retains viral ribonucleoproteins in

the nucleus,[94] but also significantly suppresses HCMV replications in primary human fibroblast cells (IC_{50}: 130 nM).[89] Furthermore, sorafenib is an approved anticancer compound that inhibits VCP in the cellular secretory pathway, thereby impeding the viral egress of Rift Valley fever virus.[96]

1.3.3.2 AMPK

Adenosine monophosphate-activated protein kinase (AMPK) is an intracellular serine/threonine kinase activated by metabolic stresses to promote catabolic pathways or suppress biosynthetic pathways.[97] AMPK plays a multifaceted role in viral infections: (i) beneficial effects in that AMPK activation inhibits viral infections such as HIV, HBV, HCV, HSV-1, VSV, influenza, human adenovirus, Kaposi's sarcoma-associated herpesvirus (KSHV), and coxsackievirus B3; and (ii) detrimental effects in that AMPK activation promotes viral infections such as dengue, RSV, Ebola, HCMV, rotavirus, and Zika infections.[97]

Many AMPK antagonists and agonists (Figure 1.2F) have been designed to prevent viral infections.[97] For instance, AMPK restricts the lytic replication of Kaposi's sarcoma-associated herpesvirus, while two AMPK agonists, metformin and AICAR, inhibit the expression of viral lytic genes.[98] A small compound called PF-06409577 activates AMPK to reduce viral infections of Zika, dengue, and West Nile virus.[99] Moreover, the AMPK–mTOR pathway promotes RSV replication, but a small AMPK inhibitor (compound C) can effectively block the viral replication.[100]

1.3.3.3 AAK1 and GAK

Adaptor-associated kinase 1 (AAK1) and cyclin G-associated kinase (GAK) are cellular kinases that regulate trans-Golgi network (TGN) transport and clathrin-mediated endocytosis.[101] Both AAK1 and GAK are serine/threonine kinases that phosphorylate specific threonine residues in clathrin-associated adaptor protein complexes, thereby enhancing their binding to tyrosine signals in cargo proteins and stimulating vesicle assembly and internalization.[102] AAK1 and GAK take part in the life cycle of many viruses such as HCV, dengue, Zika, and Ebola.[102,103] In addition to their important role in HCV cell-to-cell transmission,[103] AAK1 and GAK activate cellular proteins (*e.g.* AP2M1, EGFR, NUMB) to regulate viral entry.[104]

Many compounds have been designed to target AAK1 and GAK (Figure 1.2G and H). The combination of two approved anticancer kinase compounds, sunitinib and erlotinib, can inhibit AAK1- and GAK-regulated viral trafficking and provide the sustained suppression of dengue and Ebola infections.[101] In dengue-infected mice, the inflammatory cytokine responses are altered by sunitinib plus erlotinib treatment.[105] As a novel AAK1 inhibitor, pyrrolo[2,3-*b*]pyridine effectively inhibits dengue infections in primary dendritic cells.[102] Despite the above findings, novel AAK1 and GAK inhibitors (*e.g.* gefitinib) still require clinical evaluations.

1.3.4 Other Host Proteins

1.3.4.1 BRD4

The Bromodomain and Extra-Terminal Domain (BET) family includes five proteins (BRD1, BRD2, BRD3, BRD4, BRDT) that target acetylated lysine in histones and other proteins to coordinate the recruitment of transcriptional complexes to human chromatin.[106] BET proteins play a key role in regulating the gene expression of many viruses (*e.g.* HIV, HPV, murine leukemia virus, Kaposi sarcoma-associated herpesvirus).[107] For instance, the gene expression of Epstein–Barr virus (EBV) is modulated by BRD4, while BET inhibitors (*e.g.* JQ1) can reduce BRD4 recruitment (Figure 1.2I), thereby preventing viral gene expression.[108] Furthermore, BRD4 is an epigenetic reader in the regulation of HIV transcription, and a small compound ZL0580 targeting the BD1 domain of BRD4 induces the suppression of HIV-1 transactivation and transcription elongation.[109] Two BET inhibitors (JQ1, CPI-203) can inhibit tumor growth and reduce the mRNA expression of BATF3 and MYC – two important proteins that cooperatively drive the gene expression of adult T cell leukemia/lymphoma associated with human lymphotropic virus type 1 (HTLV-1).[110] Furthermore, BRD4 interacts with the viral E2 protein of human papillomavirus with a high affinity, and the BET inhibitor I-BET762 can effectively reduce the viability of papillomavirus 16 (HPV-16).[111] Many BET inhibitors have been developed to treat cancers,[106] but their applications in antiviral treatment still require *in vivo* experiments.

1.3.4.2 RACK1

Receptor for activated C kinase 1 (RACK1), a member of the WD40 protein family, acts as a scaffolding protein to recruit other effector proteins (*e.g.* protein kinase C) in many cellular processes and pathways.[112] Moreover, RACK1 binds to a highly conserved cradle in the 40S ribosomal subunit based on specific interactions with both ribosomal RNA and proteins. Many viruses (*e.g.* HIV, HCV, HSV) use RACK1 to translate viral mRNA using the Internal Ribosomal Entry Site (IRES) in the secondary structure of mRNA.[113] As a cofactor of dengue NS1 protein, ribosomal protein RACK1 is essential for viral RNA amplification and the initial translation of dengue RNA.[114] The inhibition of RACK1 strongly impairs the replication of dengue[114] and hepatitis E.[115] During the life cycle of poxvirus vaccinia virus, RACK1 regulates viral mRNA translation and viral kinase B1 phosphorylates serine/threonine residues in RACK1 to enhance the activity of viral polyA-leader.[116] Moreover, RACK1 interacts with the virus-induced signaling adaptor to downregulate virus-induced IFN-β production.[117] For this reason, RACK1 inhibitors may prevent the viral proliferation of many viruses. A small compound SD-29 and its analog SD-29-14 target the phosphorylation pocket of RACK1, thereby inhibiting HSV-1 gene expression and proliferation in Hep-2 cell lines.[113] Further clinical studies are still required.

1.3.4.3 Hsp27

Heat shock protein 27 (Hsp27), encoded by the HSPB1 gene, is an intracellular chaperone with multiple functions in many pathophysiological pathways. HSP27 in its oligomeric structure (Figure 1.2I) not only promotes cancers,[118] but also takes part in the life cycle of human viruses such as HCMV,[119] Enterovirus 71,[120] and HIV.[121] For instance, a rapid upregulation of Hsp27 is required for the survival of HCMV-infected monocytes.[119] Hsp27 promotes the activities of the internal ribosome entry site, thereby regulating the viral translation of Enterovirus 71.[122] As a novel Hsp27 inhibitor isolated from a traditional Chinese herb, TDP (1,3,5-trihydroxy-13,13-dimethyl-2*H*-pyran [7,6-*b*] xanthone) significantly protects against cytopathic effects and inhibits Enterovirus 71.[122] Many Hsp27 inhibitors such as apatorsen (OGX-427), brivudine, imatinib, actinomycin D, MAA, and quercetin have been proposed as anticancer agents,[123] but these inhibitors may also potentially inhibit viral infections.

1.4 Viral *Versus* Host Targets

1.4.1 Strengths and Weaknesses of Viral Targets

In most cases, antiviral agents targeting viral proteins have better safety profiles than those targeting host proteins, because viral-targeted compounds may exert less impact on human immune responses. As of August 2019, most approved antiviral agents (97%, 81/83) target viral proteins, and most of them are enzymes such as viral proteases and viral polymerases. These approved inhibitors can interfere with a specific stage of the viral life cycle such as viral entry, viral replication, viral transcription, or viral budding.[124,125] Furthermore, most antiviral candidates in the pipeline of pharmaceutical companies target viral proteins, except for a few host-targeted agents (GS-9688, GS-4224, vesatolimod) in phase 1 or 2 trials.

Antiviral inhibitors targeting viral proteins are prone to drug resistance and cross-resistance because human viruses are usually characterized by high diversity and mutation rates. Although combination treatments may significantly reduce viral loads, many human viruses (*e.g.* HIV) are still incurable due to the emerging drug resistance that induces treatment failure.[126] Moreover, antiviral agents may effectively reduce viral loads below the detection limits, but some viruses could still hide in host cells to escape antiviral inhibition. For instance, current HBV therapies can effectively reduce HBV viral loads, but they cannot remove the covalently closed circular DNA (cccDNA) of HBV in the hepatocyte nucleus, which can continue to cause viral infections.[124]

1.4.2 Strengths and Weaknesses of Host Targets

Host-targeted therapies exert strong inhibition against viral strains that are resistant to virus-targeted inhibitors because human proteins are often conserved without the risk of drug resistance and cross-resistance. As the first approved CD4-directed post-attachment inhibitor, Ibalizumab blocks

HIV entry and preserves the normal immunological functions.[75] Ibalizumab shows strong antiviral activities in multidrug-resistant HIV-infected patients who have limited treatment choices.[127]

One host-targeted therapy may exhibit broad-spectrum inhibition against many human viruses because host proteins are commonly hijacked by different human viruses during the viral life cycle. For this reason, it is believed that host-targeted drugs not only simplify current therapies to treat co-infections but also facilitate the management of emerging and re-emerging infectious diseases.

Host-targeted antiviral inhibitors may face the challenge of a low degree of selectivity and safety. First, it is almost impossible to precisely deliver antivirals to the infected cells alone, while non-specific inhibitions could cause a catastrophe to many cellular proteins in normal cells. Second, host-targeted inhibitors may interfere with important activities of host proteins that usually take part in various cellular pathways, thereby causing unexpected adverse events.[124] Third, host-targeted inhibitors can only target host proteins that are hijacked by active viruses, but not latent viruses. Latent viruses such as HIV and HSV can sleep in host cells for a long time, thereby limiting the use of host-targeted inhibitors to eliminate virus-infected cells. As of August 2019, only two host-targeted antivirals (maraviroc, Ibalizumab) have been approved for HIV treatment. Therefore, it remains important to develop effective host-targeted antivirals with favorable safety profiles.[128]

1.5 Conclusion

Many viral and host targets have been explored to develop antiviral drugs with different mechanisms of drug action. Both strategies have their pros and cons which should be taken into account during the developmental stage of new antiviral agents. On the other hand, repurposing approved drugs can reduce clinical risks and save development costs, because different human viruses may share similar drug targets or viral pathways.[3,129,130] For instance, ribavirin might be considered for treating Hendra and Nipah virus infections, while cidofovir might be used for treating human polyomavirus, adenovirus, and smallpox.[1] Moreover, favipiravir and sofosbuvir showed potential activity against Ebola and Zika virus.[129] Nitazoxanide approved as an antiparasitic drug is currently evaluated in phase 2 or 3 clinical trials to treat influenza (NCT03336619; NCT01610245), HBV (NCT03905655), HCV (NCT01197157), and respiratory virus infections (NCT02057757).

Since a large number of human viruses are incurable, it is critical to explore both viral and host targets for the treatment of current and emerging viral infections in the global population.

Conflicts of Interest

The authors disclose no conflicts.

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