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Review

Antiviral PROTACs: Opportunity borne with challenge

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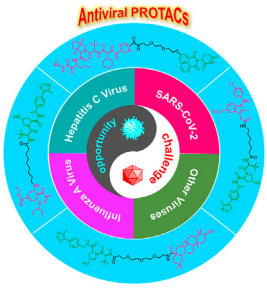
GRAPHICAL ABSTRACT



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ABSTRACT

Proteolysis targeting chimera (PROTAC) degradation of pathogenic proteins by hijacking of the ubiquitin-proteasome-system has become a promising strategy in drug design. The overwhelming advantages of PROTAC technology have ensured a rapid and wide usage, and multiple PROTACs have entered clinical trials. Several antiviral PROTACs have been developed with promising bioactivities against various pathogenic viruses. However, the number of reported antiviral PROTACs is far less than that of other diseases, e.g., cancers, immune disorders, and neurodegenerative diseases, possibly because of the common deficiencies of PROTAC technology (e.g., limited available ligands and poor membrane permeability) plus the complex mechanism involved and the high tendency of viral mutation during transmission and replication, which may challenge the successful development of effective antiviral PROTACs. This review highlights the important advances in this rapidly growing field and critical limitations encountered in developing antiviral PROTACs by analyzing the current status and representative examples of antiviral PROTACs and other PROTAC-like antiviral agents. We also summarize and analyze the general principles and strategies for antiviral PROTAC design and optimization with the intent of indicating the potential strategic directions for future progress.

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1. Introduction

Viruses are noncellular microorganisms that can contain a complete genome and diverse proteins or only infectious RNA (viroid and virusoid) (Villarreal, 2011) and as pathogens cause a severe economic and public health burden worldwide (Choi, 2021). Currently >70% of infectious diseases are caused by viruses, and several viruses had caused several serious epidemics. For example, smallpox, one of the earliest and most devastating infectious diseases, caused by the variola virus resulted in 300–500 million people death in the 20th century alone (Mühlemann et al., 2020); "Spanish flu," caused by influenza H1N1 strain, resulted in 25–100 million death cases in 1918 (Basler, 2007; Mills et al., 2004); the Ebola epidemic (2014), caused by the Ebola virus, had a 25%–90% fatality rate (Furuyama & Marzi, 2019); severe acute respiratory syndrome (SARS) caused by the SARS-coronavirus (CoV) (Dyall et al., 2017; Skowronski et al., 2005), had thousands of infection cases; Middle East respiratory syndrome caused by MERS-CoV (Millet & Whittaker, 2015) had a 35% fatality rate; and the very recent coronavirus disease 2019 (COVID-19), initially reported in China, and caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Ling et al., 2020), led to approximately 759 million infections and 6.8 million deaths (WHO, 2023).

Generally, vaccination is an effective means of preventing virally transmitted diseases and can significantly reduce the risk of infection and serious complications. Fortunately, the discovery of vaccinia viruses enabled the complete eradication of smallpox by 1980 (Quach et al., 2022). At present, there are three types of licensed seasonal influenza vaccines, including inactivated, live-attenuated, and recombinant hemagglutinin (HA) vaccines (Trombetta et al., 2022). In 2019, the European Medicines Authority and the United States Food and Drug Administration (FDA) approved the first Ebola vaccine, ERVEBO™, to help control the outbreak (Wolf et al., 2021). A range of vaccines has been approved for prophylaxis of SARS-CoV-2 infection, including the inactivated, mRNA, and viral vector vaccines. Diverse vaccines have been licensed for preventing the diseases caused by these high pathogenic viruses (except for the SARS-CoV and MERS-CoV); however, these constitute an extremely small proportion of viruses that infect humans, and the protection provided by vaccines is limited, especially as with the emergence of virus variants. For example, the approved SARS-CoV-2 inactivated vaccines are less effective in protecting individuals due to the frequent emergence of novel variants carrying mutations, such as Omicron (Chen et al., 2022; Feikin et al., 2022; Yang, 2021).

In addition to antiviral vaccines, nearly a hundred diverse antiviral drugs have been discovered and approved as idoxuridine (IDU) was approved as a first small-molecule inhibitor for the clinical treatment of virus infection (Ravin et al., 1964), human society still faces serious challenges due to newly emerging viruses that lack treatment options and the known viruses with resistance to approved drugs (Lozano et al., 2012). Therefore, extensive efforts have been devoted to the development of antiviral drugs associated with potent efficacy and specific mechanism of action (Goncalves et al., 2021), including covalent inhibitors, immuno-regulators, monoclonal antibodies, host cell killing agents, and others (De Clercq & Li, 2016). However, most of these antivirals have been proven to exhibit various side effects, including high off-target, toxicity gastrointestinal tract reactions, hepatotoxicity, nephrotoxicity, cardiotoxicity, and myelosuppression (Attia et al., 2018; Lembo & Cavalli, 2010; Linnakoski et al., 2018). Furthermore, the error-prone replication machinery of many virus strains make them prone to mutation and thereby resistant to current antiviral drugs (Hughes & Andersson, 2015). Thus, highly specific and effective antiviral agents with a unique mechanism of action are urgently required to combat viral infections that pose a serious threat to human health (Cele et al., 2022).

In contrast to the traditional inhibitors that adopt an "occupancy-driven" mode, the proteolysis targeting chimeras (PROTACs) are a newly emerging strategy of targeted protein degradation (TPD) for drug discovery that possess a distinct mechanism of action to enable treatment (Adjei, 2006; Pettersson & Crews, 2019). A PROTAC is a type of heterobifunctional compound compromising a protein of interest (POI) ligand, linker, and E3 ligase ligand (Fig. 1), which can be designed and synthesized according to different needs or purposes. First, the POI ligand binds to the pathogenic protein, then the E3 ligand connected to the other terminus of the linker recruits the corresponding E3 ligase to the proximity of POI to subsequently induce the polyubiquitination of the target protein. Finally, the polyubiquitinated protein is recognized and degraded by the 26S proteasome (Dale et al., 2021; Pettersson & Crews, 2019).

As the first peptide-based PROTACs were reported to degrade methionine aminopeptidase 2 (MetAP-2) by Crews et al., in 2001 (Sakamoto et al., 2001), the mechanism of action of complete target degradation enabled the successful application of PROTACs in many areas of drug development, and the number of papers related to PROTAC research has grown significantly since 2018 (Fig. 2A) (Dale et al., 2021; Ermondi et al., 2021), and >130 proteins, involved in cancer, leukemia, cardiovascular disease, neurodegenerative disease, and virus infection (e.g., hepatitis C virus (HCV) NS3/4A PROTAC DGY-08-097 (**1**) in Fig. 2B) have been targeted for degradation by corresponding PROTAC compounds (He et al., 2022). In the development of antitumor drugs in particular, several PROTACs for malignant tumor treatment were developed as candidates for clinical trials; for instance, ARV-110 (**2**) (an androgen receptor-targeted PROTAC for prostate cancer) and ARV-471 (**3**) (an estrogen receptor-targeted PROTAC for breast cancer) developed by Arvinas are in phase II clinical trials; in addition, DT2216 (**4**) (a BCL-X_L degrader for hematomas and solid tumors) developed by Dialectic Therapeutics is in a phase I clinical trial (Fig. 2B) (Halford, 2021; Neklesa et al., 2018, 2019).

With the rapid and successful development of diverse PROTAC-based treatment options, the PROTAC technology has gradually entered the field of antiviral drug research (de Wispelaere et al., 2019). Essentially, the concept of TPD has been shifted from the hijacking of the ubiquitin-proteasome system (UPS) by the virus to the virus itself and targeting its proteins for degradation (Bekes et al., 2022), and has subsequently attracted substantial attention from academia and industry following the outbreak of COVID-19 (Desantis et al., 2021; Haniff et al., 2020). The successful application of PROTACs for antivirals may break through the bottleneck of antiviral drug discovery and provide a more available solution to tackle the pandemic. However, many problems are associated with PROTACs, and the application in the field of antivirals faces numerous challenges (Fang et al., 2022; Gao et al., 2020; Zeng et al., 2021).

In this review, we will provide a systematic and detailed introduction of the recently reported antiviral PROTAC cases from the perspective of

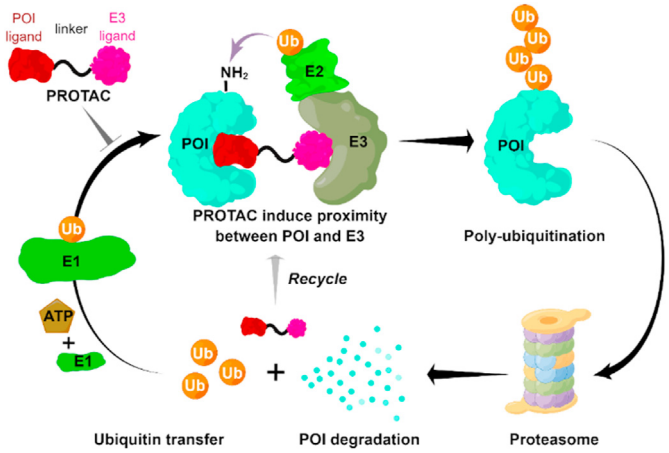

Fig. 1. Schematic diagram of the mechanism of action of PROTACs.

design strategy and the potential challenges, which are likely to benefit and direct the development of antiviral degraders. In addition, other similar PROTAC-like antiviral degraders will also be discussed.

2. The dilemma of traditional antiviral small-molecule inhibitors

As exogenous pathogens, viruses possess a unique and precise life cycle for the production of progeny virus particles (Koonin et al., 2022). In general, the life cycle of a virus is composed of six vital different stages: attachment, penetration, uncoating, replication, assembly, and virion release (Liang et al., 2020), and viral proteins and host factors involved in these stages play important roles in driving efficient and accurate viral replication (Fig. 3) (Goncalves et al., 2021). Therefore, several direct-acting antivirals and host-targeting antivirals have been approved for treatment of viral infections during recent decades (De Clercq & Li, 2016). Nevertheless, antivirals remain lacking for several viruses with high pathogenicity to humans (Matthew et al., 2021), even though several of them have been known for years, such as the Ebola virus (Illescas et al., 2017), Marburg virus (Schafer et al., 2021), dengue virus (Kaptein et al., 2021), and SARS-CoV (Pruijssers et al., 2020). Unfortunately, a significant number of the approved drugs have developed resistance problems caused during long-term clinical treatment and the frequent appearance of mutant variants (Matthew et al., 2021). For example, amantadine, which was approved by the FDA as a treatment option for influenza A virus (IAV) in 1966, has lost most of the inhibitory activity against IAV due to the mutation of the M2 ion channel protein of IAV, and consequently, this drug is no longer recommended for the therapy of influenza by the FDA (Bright et al., 2006; Jalily et al., 2020; Tzitzoglaki et al., 2017). Similarly, another clinical first-line therapy drug, oseltamivir, is losing its efficacy against IAV due to the emergence and spread of the IAV H274Y strain (Tang et al., 2019). Specifically, the mutation of histidine to the bulkier tyrosine amino acid can disturb the hydrophobic pocket formed by the methylene of Glu276, thus dramatically attenuating the interaction between oseltamivir carboxylate and the catalytic site of neuraminidase (NA) (Collins et al., 2008). Except for the severe drug resistance of influenza viruses, both the human immunodeficiency virus and HCV are also resistant to clinical antiretroviral therapies (Blassel et al., 2021) and protease inhibitors (Kim et al., 2016), respectively. In contrast to traditional inhibitors that depending on the high binding affinity to the POI, "even driven" PROTAC molecule have considerable advantages toward mutated targets (Pettersson & Crews, 2019). Once the PROTAC can attach the POI and simultaneously recruit the E3 ligase into the proximity of the target, the latter will be completely destroyed by the proteasome after it has been modified by polyubiquitination, which does not need high affinity binding between the PROTAC and POI (Liu et al., 2022). In addition, the released PROTAC molecules can then perform a new round of catalytic degradation of the target (Fig. 1) (Pettersson & Crews, 2019). Thus, PROTACs are promising candidates to fight against the dilemma of drug resistance, low selectivity, and high toxicity of current antiviral drugs.

3. The emergence of antiviral PROTACs

3.1. Peptide-based PROTACs against hepatitis B virus

The X-protein (154 amino acid, 17 kDa) of the hepatitis B virus (HBV) is crucial for virus infection and contributes to the development of HBV-induced cirrhosis or even hepatocellular carcinoma (HCC) in patients chronically infected with HBV. Consequently, almost 1 million people die from cirrhosis and HCC secondary to HBV infection ever year (Nannini & Sokal, 2017; Xie et al., 2018), whereas only a small percentage of patients chronically infected with HBV achieve a functional cure (Gane, 2017; Papatheodoridi et al., 2022). Therefore, inducing the degradation of the X-protein and antagonizing its function may be effective in treating HBV infection and/or prevention of HCC.

In 2014, Montrose et al. reported the first research focused on the applicability of PROTAC technology to decrease the abundance of a virus-related protein and demonstrated that a novel cell-permeable PROTAC antagonized and destroyed the X-protein of HBV (Montrose & Krissansen, 2014). In this study, the PROTAC was constructed by tethering the N-terminal oligomerization domain with C-terminal instability domains of the X-protein and making it cell-permeable by N-terminal

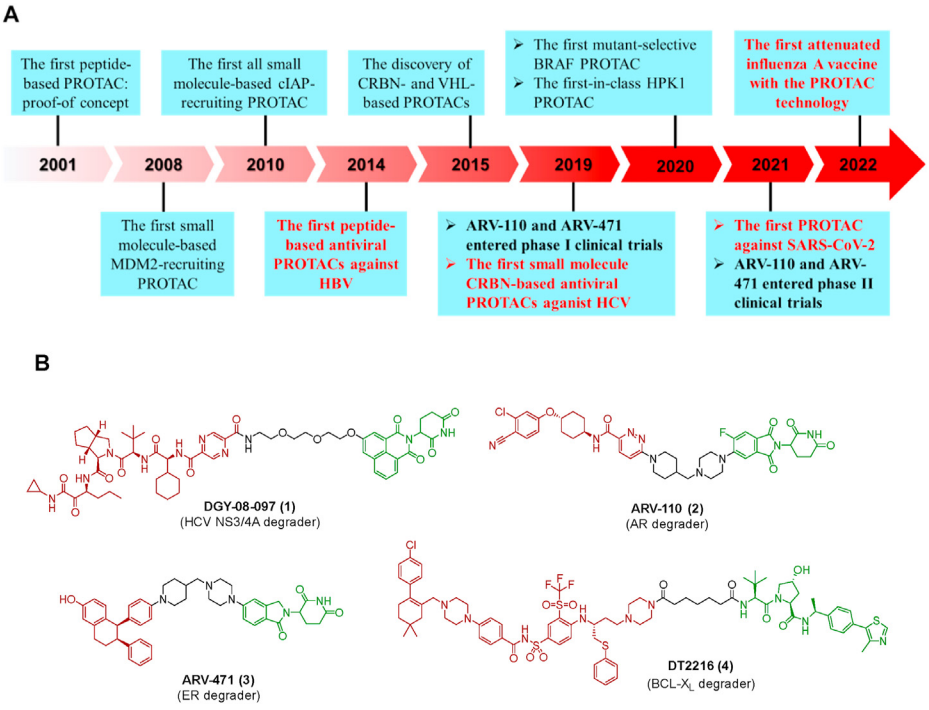

Fig. 2. A) Development timeline of PROTACs; B) The first small-molecule antiviral PROTAC DGY-08-097 (**1**), and representative antitumor PROTACs ARV-110 (**2**), ARV-471 (**3**), and DT2216 (**4**) currently in clinical trials.

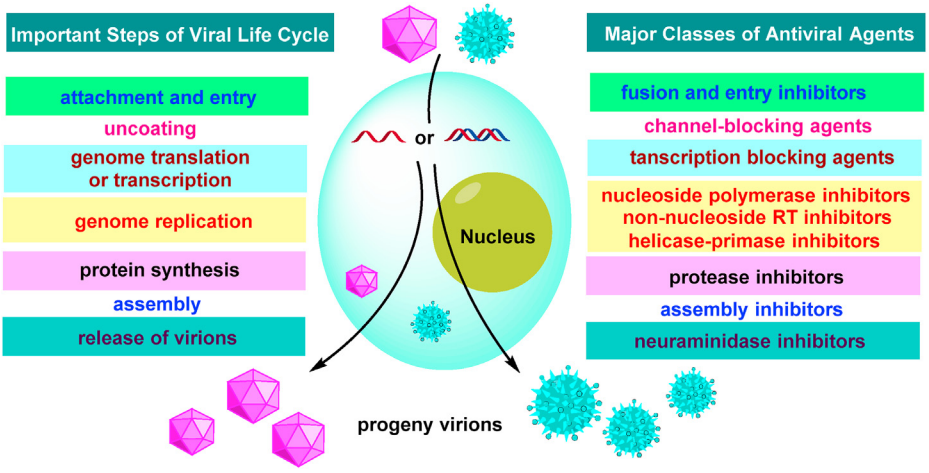

Fig. 3. The general life cycle of viruses and targets for antiviral agents.

fusion to a polyarginine cell-penetrating peptide (Rodriguez-Gonzalez et al., 2008) (Fig. 4). Experimentally, the oligomerization domain bound to the X-protein, and the unstable region caused the X-protein to become a misfolded or damaged target suitable for degradation by the UPS. Furthermore, the oligomerization domain of the PROTAC was verified to antagonize the proapoptotic function of X-protein (Fig. 5). Nevertheless, this peptide-based PROTAC has not been further investigated for inhibition of HBV replication and the progression of chronic hepatitis, which limit its application in the field of anti-HBV treatments.

3.2. NS3/4A-targeted PROTACs against HCV

HCV is a positive single-strand RNA virus that undergoes a long latent period causing a series of progressive infection syndromes, such as liver fibrosis, cirrhosis, and even cancer, and has consequently become a threat to public health. A HCV polyprotein undergoes proteolytic processing to form 10 structural and nonstructural proteins (Chigbu et al., 2019; Lahm et al., 2002; Timiri et al., 2016; Zhang et al., 2017). Among these viral proteins involved in HCV replication, the NS3/4A complex protein is a multifunctional enzyme with N-terminal serine protease domain and C-terminal helicase domain. This enzyme catalyzes the cleavage of HCV polyprotein precursors to produce numerous vital

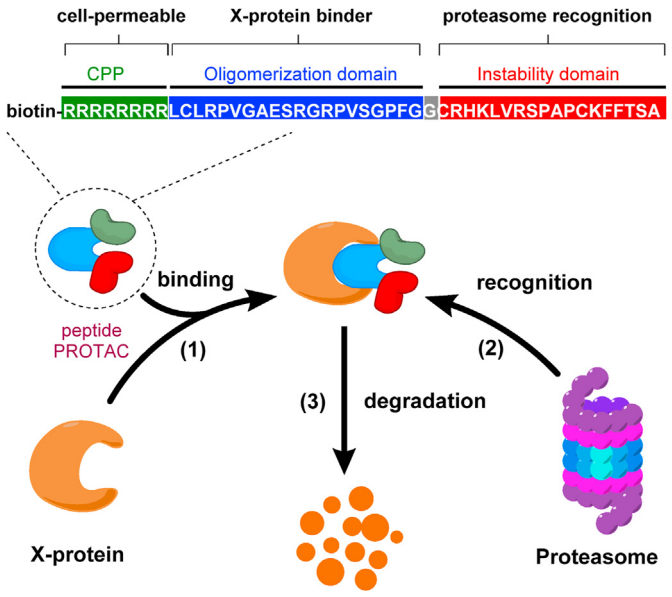

Fig. 4. The discovery of an HBV X-protein targeting PROTACs based on peptide.

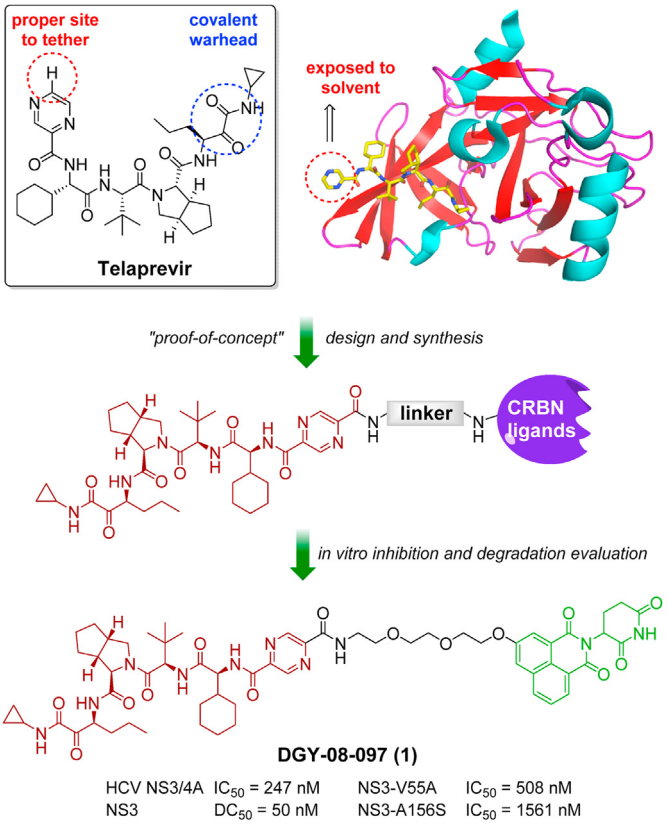

Fig. 5. The crystal structure complex of telaprevir with HCV NS3/4A and structures of representative HCV NS3/4A-targeted PROTACs.

mature nonstructural proteins (NSPs), such as serine proteases, helicases/nucleotide triphosphatases, and RNA-dependent RNA polymerases (RdRp) (McCauley & Rudd, 2016; Tran et al., 2020). The NS3/4A protease also cleaves cellular proteins, such as MAVS and TRIF, two host proteins involved in cellular immune response initiation (Horner & Gale, 2013). Up to now, only the NS3/4A protease has been successfully used as a DTA target. The first-generation small-molecule inhibitor, telaprevir (VX-950) could covalently bind to the serine residue in the catalytic site of NS3/4A. However, the low drug resistance barrier of telaprevir produced a dramatic loss of the antiviral activity against HCV (Hézode et al., 2009; Lin et al., 2004; Sarrazin et al., 2007).

In 2019, Yang et al. reported that small-molecule PROTACs against

HCV induced NS3/4A degradation *in vitro* and was the first case to fuse PROTAC technology with an antiviral small-molecule inhibitor as a ligand of a POI (Fig. 5) (de Wispelaere et al., 2019). This study conducted a detailed analysis of the HCV NS3/4A-Telaprevir co-crystal structural complex (PDB: 3SV6) and found that the pyrazine group was a solvent-exposed fragment, which enabled this to act as a tethering site. Next, a series of heterobifunctional compounds were designed and synthesized by conjugating the telaprevir to different CRBN ligands using alkyl or PEG polymers to confirm whether the PROTACs technology could be applied to combating viruses as a credible novel antiviral strategy. As expected, these conjugators not only maintained the capability to inhibit the NS3/4A protease with IC_{50} values ranging from 247 to 385 nM but they also successfully engaged the $CRL4^{CRBN}$ complex. Furthermore, these bifunctional degraders significantly induced rapid and sustained proteasome-mediated NS3 protein degradation in a concentration-dependent manner in a cultured cell line. Compound **DGY-08–097** (**1**) had the higher efficacy to induce NS3 degradation via the UPS pathway with a DC_{50} value of 50 nM, although yet reduction in the neo-substrate abundance of IMiDs (IKZF1 and IKZF3) has not been detected as a novel tricyclic imide moiety was chosen as the highly specific CRBN ligand. Consistent with many other PROTACs that can overcome mutational variation in cancers, compound **DGY-08–097** (**4**) could also degrade the NS3–V55A and NS3-A156S variants resistant to telaprevir and exhibited inhibition activity against these two protease mutants with IC_{50} values of 508 and 1561 nM, respectively, which was only three-fold higher than that of wild-type NS3. Interestingly, HCV NS3/4A-targeted telaprevir was recently found to target and inhibit the 2A protease of enterovirus D68 (Musharrafieh et al., 2019), suggesting that this PROTAC molecule could degrade the EV-D68 2A protease and exhibit anti-EV-D68 activity. Although these findings only demonstrated the antiviral superiority of PROTAC at the cellular level, they firmly confirmed that this emerging technology could be used as a potential method for the discovery of antivirals.

3.3. Indomethacin-based PROTACs against SARS-CoV-2

Since the COVID-19 pandemic, several promising several direct-acting antiviral candidates have been approved for patient treatment, such as remdesivir (Lamb, 2020), nirmatrelvir (Lamb, 2022), and molnupiravir (Brophy, 2022), although their treatment effects still need to be determined in clinical settings. As an effective and rapid method for drug discovery, a "drug repurposing" strategy was also applied to screen available approved drugs to combat COVID-19 (Batalha et al., 2021; Xu et al., 2021). This found that the nonsteroidal anti-inflammatory drug (NSAID) indomethacin (INM) can combat a series of coronaviruses including canine coronavirus, SARS-CoV-1, and SARS-CoV-2 (Chakraborty et al., 2022; Marinella, 2020; Zeng et al., 2020), resulting in a phase II clinical trial for treatment of patients with mild COVID-19 symptoms (NCT04344457). Although the detailed mechanism of action of INM as a NSAID has not yet been understood, this has proven effective in many kinds of other syndromes because of the analgesic and antipyretic properties (Rao et al., 2010). INM has been reported as a potent human prostaglandin E synthase type 2 (PGES-2) inhibitor with nanomolar inhibition activity against SARS-CoV-2 (Al-Horani & Kar, 2020). PEGS-2 was believed to play an important role in viral replication, exemplified by the fact that PGES-2 bound to viral NSP7 during the replication (Gordon, Jang, et al., 2020; Gordon, Hiatt, et al., 2020). In 2021, Goracci et al. reported a series of INM-based PROTACs against pan-coronaviruses with EC_{50} values between 18.1 and 29.8 μM. However, the systematic structure–activity relationship (SAR) and mechanism of action of these INM-based conjugates need further exploration to assess whether the enhancement of inhibitory activity of these conjugates is derived from the target degradation or inhibition.

Many host proteins play vital roles in the process of viral infection or replication. Thus, host-targeted PROTACs are theoretically effective therapeutic options for virus infection. However, unlike exogenous viral proteins, host proteins will have basic physiological functions, and the rapid degradation of these proteins may pose several unknown risks. Therefore, the feasibility of antiviral PROTACs targeting host protein degradation remains controversial, and more experimental data are needed to verify this.

3.4. The direct-acting antiviral PROTACs against IAV

3.4.1. Neuraminidase-targeting PROTACs

Influenza neuraminidase (NA), a mushroom-like tetramer membrane glycoprotein, is incorporated into the influenza virus envelope by a hydrophobic, single-stranded mosaic of 29 amino acids near the N-terminus (Ferraris & Lina, 2008; Gamblin & Skehel, 2010; Varghese et al., 1983). During influenza virus replication, NA is responsible for releasing progeny virions from the surface of infected cells by disrupting the interaction between the virion surface glycoprotein HA and the host cell membrane sialic acid receptor; this is consequently followed by infecting other host cells and accelerating the replication and proliferation of influenza virus (Wang et al., 2022). Furthermore, the high conservation of the active central site of NA makes this an important target for anti-influenza agents (Burmeister et al., 1993). However, because of the serious acquired drug resistance of the clinical IAV NA inhibitors and inspired by several studies to discover the protein degraders for HCV or SARS-CoV-2 (de Wispelaere et al., 2019; Desantis et al., 2021; Haniff et al., 2020), our group designed a series of IAV NA-targeted degraders to combat the highly pathogenic influenza virus (Xu et al., 2022).

The co-crystal structure complex (PDB: 2HU0) of oseltamivir bound to NA suggested that both the amino and carboxylic acid groups were appropriate sites for further modification consistent with the results of previous medicinal chemistry studies aimed at improving the binding affinity between the NA and oseltamivir by SAR study (Fig. 6). Hence, 22 PROTAC molecules were obtained by conjugating different E3 ligands to the two tether sites on the core scaffold of oseltamivir. Most of these conjugates exhibited parallel inhibition efficacy against H1N1 with

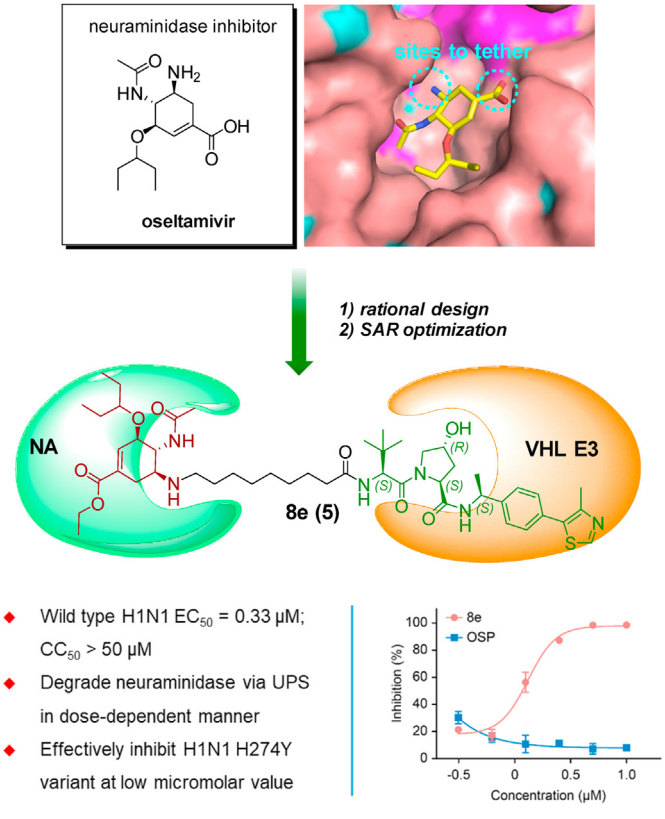

Fig. 6. The discovery of IAV NA-targeted PROTACs based on oseltamivir.

micromolar to sub-micromolar EC_{50} values compared with that of the positive control, oseltamivir phosphate. The VHL ligand-based compound **8e** (**5**) not only acted as the most effective agent to inhibit the replication of H1N1 with a EC_{50} value of 0.33 μM in MDCK cells but also induced the most significant degradation of NA in a concentration-dependent manner with a DC_{50} value at the micromolar level. However, none of the oseltamivir carboxylate-based conjugators could degrade NA associated with moderate inhibitory activity against H1N1 replication *in vitro*, indicating that the appropriate tether site was important to degradation activity. In contrast, PROTAC **8e** (**5**) had a significant advantage in inhibiting the proliferation of a H1N1 H274Y variant resistant to oseltamivir, which was most likely due to the TPD nature of the PROTAC strategy. The pharmacokinetic study in rats confirmed that compound **8e** (**5**) possessed a modest drug-like that was observed with PROTACs for other diseases (Zeng et al., 2021).

3.4.2. *Hemagglutinin (HA) targeting PROTACs*

Almost simultaneously, Zhou et al. at Peking University reported the discovery of pentacyclic triterpenoid-based PROTACs as a class of HA degraders to fight influenza (Li, Wang, et al., 2022). Based on their previous identification that an oleanolic acid (OA) derivative had a micromolar IC_{50} value against strain A/WSN/33 and to confirm the "proof of concept" of antiviral PROTACs, they next selected the carboxyl acid group on the OA derivative as a tether site and conjugated this with thalidomide or VHL ligand to construct a series of heterobifunctional compounds for SAR analysis (Fig. 7A). These PROTACs could bind to both the HA and E3 ligase, of which the compound **V3** (**6**) had micromolar binding affinity to the HA protein with a K_D value of 3.18 μM. As expected, compound **V3** (**6**) could deplete HA with a DC_{50} value of 1.44 μM in a concentration-dependent manner via the UPS pathway in 293T cells infected with influenza virus, and the degradation was completely abolished by the treatment with MG-132 and VHL ligand or by transfection with siRNA-VHL. Interestingly, PROTAC **V3** (**6**) was ineffective at inhibiting the HA and interfering with the entry of pseudovirus, and a detailed binding site study revealed that the OA fragment targeted an inactive site rather than the catalytic sialic acid binding pocket on the HA protein. This specific mode-of-action of **V3** (**6**) enables the degradation of HA-associated proteins without inhibitory HA activity, and can therefore abolish the replication of IAV (Fig. 7B). These findings validated the advantage of the PROTAC strategy for targeting undruggable sites of viral proteins. Compound **V3** (**6**) also exhibited broad-spectrum antiviral activities against two different H1N1 strains and one H3N2 strain with EC_{50} values ranging from 4.53 to 8.98 μM, while showing no inhibitory activity against influenza B virus. Although the bioavailability of compound **V3** (**6**) was only approximately 6.8%, this was sufficient to produce a survival rate in infected mice of 100% at a dose of 10 or 20 mg/kg via intravenous injection, indicating the high potency of PROTACs for virus infection treatment.

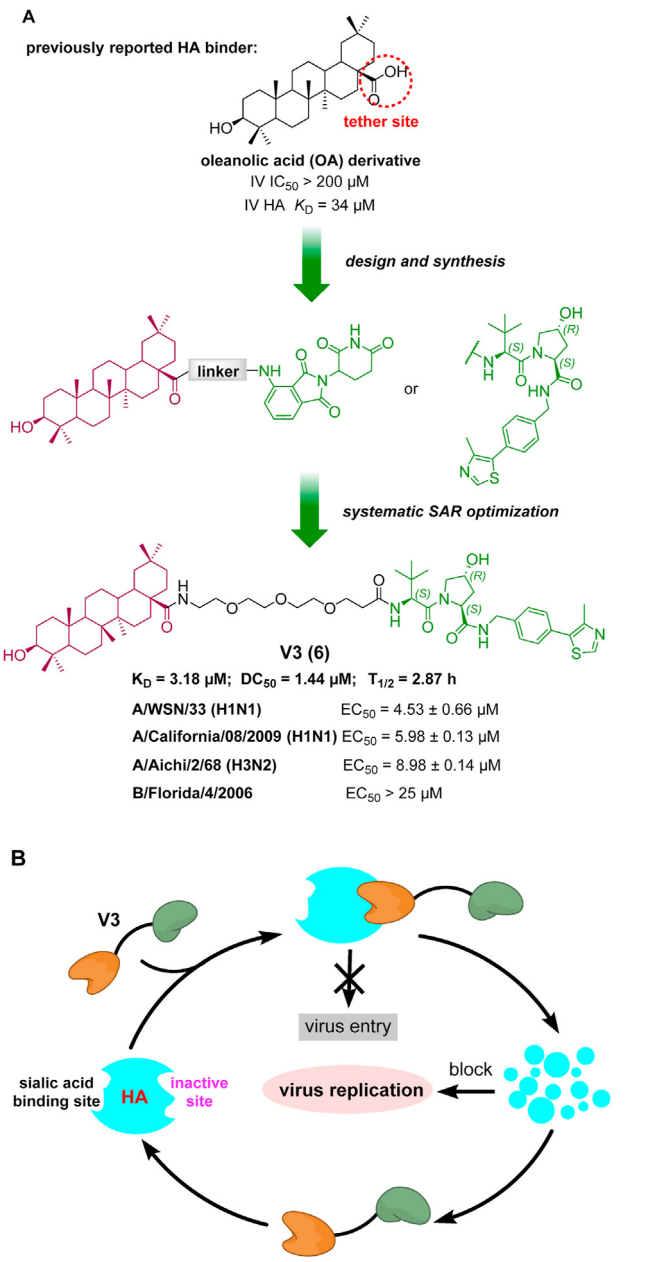

Fig. 7. A) Discovery of IAV HA-targeted PROTACs; B) The mechanism of action of representative PROTAC V3 (**6**).

3.5. *CDK-targeted PROTACs against human cytomegalovirus*

As a class of attractive targets for the discovery of antitumor drugs, cyclin-dependent kinases (CDKs) are known to be involved in the proliferation of cancer cells (Cheng et al., 2019; Latif et al., 2016; Lin et al., 2018). CDKs were discovered as vital factors that participate in the replication of many viruses, including human cytomegalovirus (HCMV) (Feichtinger et al., 2011; Graf et al., 2016). Many inhibitors to CDK1, 2, 7, and 9 have been discovered as well as pan-CDK inhibitory compounds that showed significant inhibition activities against CMV both *in vitro* and *in vivo* (Hutterer et al., 2015; Sonntag et al., 2019). Large studies have proven that these CDK-targeted inhibitors displayed a broad-spectrum antiviral activity and could enhance the treatment effect during the drug combination (Hutterer et al., 2015; Wild et al., 2021). To confirm whether the host-targeted PROTACs could yield novel antiviral drugs, Marschall et al. evaluated CDK9-directed PROTAC, **THAL-SNS032** (**7**), degradation against CDK1, CDK2, CDK7, and CDK9, (Hahn et al., 2021). Notably, the heterobifunctional molecule was the most responsive to the CDK9 subtype compared with the CDK2 and CDK7 subtypes at a concentration of 100 nM (Fig. 8). In addition, the CDK9 PROTAC seemed to be potent in interrupting the mutual feedback loop between the HCMV-driven upregulation of CDKs and the CDK-mediated support of HCMV replication. Consistent with their hypothesis, an EC_{50} value of 0.025 ± 0.001 μM of compound **THAL-SNS032** (**7**) was determined, which was approximately four-fold lower than that of the parental

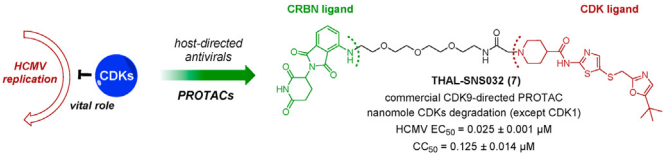

Fig. 8. The discovery of CDK-targeted anti-HCMV PROTACs.

compound SNS032.

This PROTAC also displayed an inhibitory activity against several kinds of DNA and RNA viruses, such as the murine CMV (MCMV) and the emerging SARS-CoV-2 (Table 1). **THAL-SNS032** (**7**) exerted approximately 3.7-fold stronger inhibitory activity against HCMV than that of SNS032, with an EC50 of 0.03 μM, which illustrated that this CDK9-targeted PROTAC potentially exhibited antiviral activity via a degradative mechanism. However, both the **THAL-SNS032** (**7**) and SNS032 exhibited similar inhibitory activity against MCMV or SARS-CoV-2 *in vitro*. The poor binding between thalidomide and murine CRBN could be used to explain the comparable efficacy of **THAL-SNS032** (**7**) against MCMV, although further PROTAC-based analysis of SARS-CoV-2 is still needed to illustrate this situation. The cytotoxicity of **THAL-SNS032** (**7**) was as high as that of SNS032, with a CC_{50} value of 0.18 ± 0.11 μM in HFF cells, indicated that further modification of this degrader was required to decrease the potential toxicity. This is a reminder that the off-target toxicity of PROTACs and the potential toxicity of immunomodulatory imide drugs IMiDs is an issue that cannot be ignored.

4. Other antiviral degraders

4.1. Polymerase acidic protein-targeted degrader against IAV

In 2022, a natural compound isolated from the plant endophytic fungus *Aspergillus* sp. CPCC 40073512 was identified as a potent degrader of the polymerase acidic subunit (PA) of IAV by Cen et al. (Pang et al., 2017; Zhao et al., 2022). First, natural products **APL-16–5** (**10**) and **APL-16–1** (**8**) were identified as potent anti-influenza agents with sub-micromolar EC_{50} values ranging from 0.28 to 0.36 μM during a screening assay of HEK293T cells infected with A/WSN/33, where compound **APL-16–2** (**9**) only exhibited slight inhibition of IAV (Fig. 9). Then, the most effective IAV agent, **APL-16–5** (**10**), was shown to reduce the level of the PA subunit of IAV RdRp but not the expression of PA mRNA in a concentration-dependent manner via the UPS pathway. This compound could link TRIM25 to PA and induce PA ubiquitination and proteasome-dependent degradation. However, whether its mechanism of action is similar to that of PROTACs remains unclear. Remarkably, **APL-16–5** (**10**) not only exhibited sub-micromolar antiviral activity against IAV (A/WSN/33) *in vitro* but also protected infected mice with survival rate of 100% at a dose of 20 or 100 mg/kg and reduced the severity of pulmonary inflammation.

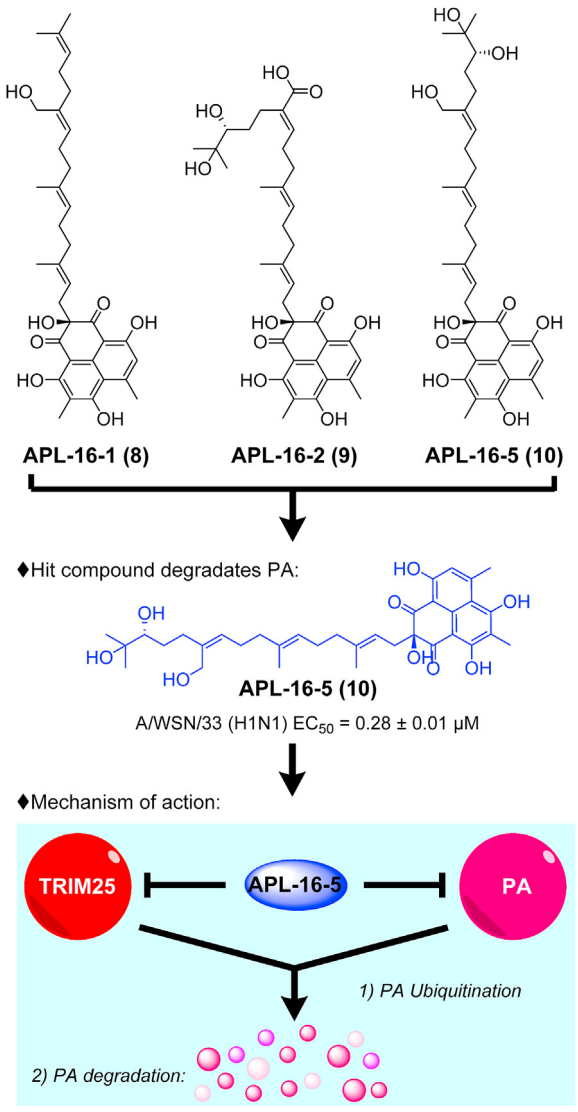

Fig. 9. The discovery of an IAV PA degrader based on microbial metabolites.

4.2. The PROTAC-based vaccine against IAV

Similar to the antiviral drugs, effective antiviral vaccines are highly anticipated to act as countermeasures with specific mechanisms of action to prevent the transmission and infection of viral pathogens by initiating the host antiviral innate immune response (Pardi & Weissman, 2020; Yang, 2021). As one of the most effective and mature prophylactic measures, live-attenuated virus vaccines can be generated by several strategies, such as cold-adapted live-attenuated influenza vaccines, codon-deoptimized virus, premature termination codon-harboring virus, hyper-interferon-sensitive virus, and viral-protein-altered virus. Nevertheless, most of these current strategies produce live-attenuated vaccines that are associated with significant or even complete loss of safety and efficacy. The immune escape of virus poses a serious challenge to the traditional influenza vaccines. It is notable that virus replication of virus is regulated by vital viral proteins to generate progeny virions, indicating that viral protein degradation is a potential method to effectively modulate the life cycle of virus for the development of a vaccine.

In 2022, Plebani et al. first combined the vaccine production strategy with the PROTAC technology to generate a live-attenuated influenza A vaccine (Fig. 10) (Si et al., 2022). PROTAC IAVs were designed by individually fusing a removable proteasome-targeting domain (PTD) to eight viral proteins, including M1, PB2, PB1, PA, NP, M2, NEP, and NS1. Specifically, the sequence of the PTD was composed of a VHL-targeting peptide, ALAPYIP, and a tobacco etch cleavage site (TEVcs) linker, ENLYFQG. However, only IAV containing a M1-PTD sequence could effectively proliferate in MDCK-TEVp cells but not in the conventional

Table 1
Broad-spectrum antiviral activities of THAL-SNS032 (7) and SNS032.

Virus	Strain/Type	Cell Type	THAL-SNS032 (9)		SNS032	
			EC_{50} (μM)	CC_{50} (μM)	EC_{50} (μM)	CC_{50} (μM)
HCMV	AD169-GFP	HFF	0.03 ± 0.01	0.18 ± 0.11	0.11 ± 0.02	0.22 ± 0.04
MCMV	Smith-GFP	MEF	0.21 ± 0.09	1.00 ± 0.22	0.29 ± 0.05	1.03 ± 0.05
SARS-CoV-2	d6-YFP	Caco-2	0.11 ± 0.02	64.9 ± 16.2	0.18 ± 0.03	59.5 ± 7.0
SARS-CoV-2 (pretreated)	d6-YFP	Caco-2	0.15 ± 0.02	64.9 ± 16.2	0.15 ± 0.03	59.5 ± 7.0

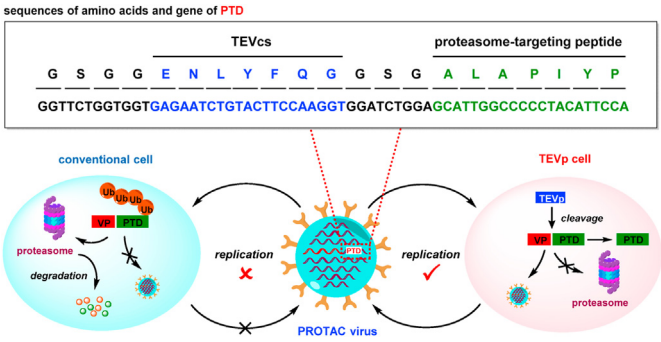

Fig. 10. The design strategy of an anti-IAV PROTAC vaccine, and the key sequence that selectively induces M1 protein degradation in conventional cells.

MDCK.2 cells, and growth of the M1-PTD virus was consequently highly attenuated in conventional cells. This elicited a robust and broad humoral, mucosal, and cellular immunity against homologous and heterologous virus challenges with extremely high safety and efficacy in mice and ferrets.

4.3. *RNA-targeted ribonuclease-targeting chimera against SARS-CoV-2*

Given that PROTAC technology has been successfully applied in basic research as well as clinical research for drug development, similar targeted degradation strategies are increasingly being developed. Among them, ribonuclease-targeting chimera (RIBOTAC) was initially adopted in 2019 to degrade a hypoxia-associated noncoding RNA (Dey & Jaffrey, 2019). Consistent with PROTACs, the RIBOTAC is a heterobifunctional molecule comprising a ligand for target RNA, a linker, and a ligand for RNase recruitment (Fig. 11). The RNA-targeted fragment of RIBOTAC first binds to the RNA of interest, and then the RNase-recruited ligand hijacks and activates RNase to cleave the substrate RNA. The released RIBOTAC can perform a new round of catalytic degradation for the target RNA. Currently, RIBOTAC has been used to degrade pre-miR-21 in TNBC and Alport symptom models (Meyer et al., 2022), and reduce c9ALS/FTD r(G4C2) repeat expansion in ALS models (Bush et al., 2021).

RIBOTAC technology was discovered to be a novel and useful method to effectively induce the SARS-CoV-2 RNA genome degradation in 2020 (Fig. 12) (Haniff et al., 2020). A convergence of structures in both coding and noncoding regions of the viral genome could be used to act as new targets for the development of small-molecule binders to inhibit the essential processes of the virus via frameshifting (Haniff et al., 2020; Pardi & Weissman, 2020). The frameshifting element of SARS-CoV-2 controls the translation of two viral precursor polyproteins, pp1a and pp1ab, which can be cleaved by PL^{pro} and M^{pro} to produce a series of

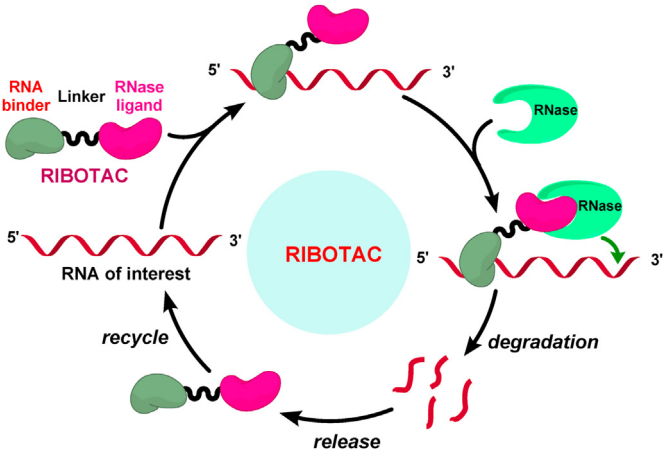

Fig. 11. Schematic diagram of the mechanism of action of RIBOTACs.

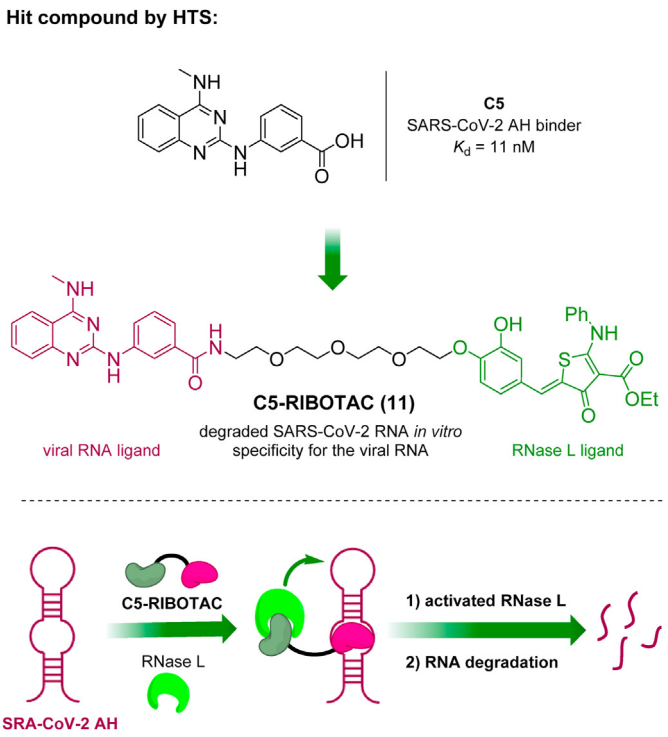

Fig. 12. The discovery of anti-SARS-CoV-2 RIBOTAC and its mechanism of action.

functional NSPs for viral replication (Lan et al., 2022; Rangan et al., 2020). Matthew D. Disney et al. designed and reported a heterobifunctional compound **C5-RIBOTAC** (**11**) to degrade the SARS-CoV-2 RNA genome based on a compound (C5) identified by screening compounds that targeted the SARS-CoV-2 attenuator hairpin (Fig. 12) (Desantis et al., 2021). Compound **C5-RIBOTAC** (**11**) caused a significant dose-dependent decrease in the level of SARS-CoV-2 RNA in HEK293T cells. These results suggest that RIBOTAC could be used as a promising strategy for combating these viruses.

5. Advantages and challenges to antiviral PROTACs

The PROTAC strategy takes advantage of a natural degradation mechanism and rapidly degrades the POI, which effectively extends the scope of targets, including several undruggable ones (Li, Song, et al., 2022), such as the transcription factors, nonenzymatic proteins, and scaffolding proteins (Sawyer, 2020). As desirable candidates, several transcription factor-targeted PROTACs (e.g., ARV-110 (**2**), ARV-476, and CFT8634) are being used to conduct clinical trials (Li, Song, et al., 2022). Protein-protein interaction (PPI) is crucial for both host cells (Rodrigues et al., 2021) and viruses (Ramage & Cherry, 2015; Torres et al., 2022) to maintain fundamental life processes, such as genetic regulation, signal transduction, and unit assembly. PPI interfaces are generally large and relatively flat, which increases the difficulty in developing strong and effective small-molecule inhibitors; however, several PROTACs can interfere with and abolish these PPIs (Hughes et al., 2021; Ma et al., 2021). In addition to targeting and destroying functional proteins, PROTACs can also exhibit therapeutic effects by deleting several nonfunctional structural proteins (Pettersson & Crews, 2019). Similarly, these advantages of PROTACs have the potential to extend the scope of antiviral targets. Antiviral PROTACs could reduce the risk of systemic toxicity and several unclear side effects by reducing administration dosage and drug exposure, due to their substoichiometric degradation function.

Notably, POI degradation induced by PROTACs does not require a strong affinity between PROTAC molecules and the POI. Consequently,

antiviral PROTACs can potentially target undruggable proteins involved in virus replication and bind the mutant proteins of a virus, thus providing a promising method to tackle this tough problem of drug resistance to antivirals. Although the formation of a POI-PROTAC-E3 ternary complex is a prerequisite for the successful degradation of the POI, this is not positively correlated with the affinity of PROTAC but is affected by the PPI between the E3 ligase and POI (Pettersson & Crews, 2019). Therefore, it remains unclear whether the low binding affinity of antiviral PROTACs for mutant POIs may result in low specificity or off-target toxicity of these heterobifunctional molecules. It is known that the acquired resistance of antitumor BET-PROTACs is primarily caused by genomic alterations that impair the core components of the associated E3 ligase complexes, and the risk of the alteration or mutation of viral POI that prevents binding to the PROTAC and potentially inducing drug resistance cannot be completely ruled out (Zhang, Riley-Gillis, et al., 2019). Fortunately, Xiong et al. reported that bridged PROTACs could induce POI ubiquitination and degradation by indirectly binding to the targeting protein's binding partner instead of directly binding to the POI (Xiong et al., 2022), which is likely to be another potential advantage of PROTACs against viral proteins that are prone to mutate.

Generally, the poor selectivity of traditional inhibitors is a common factor contributing to the high risk of off-target toxicity because of the variety of homologous proteins to their targets (e.g., CDKs and HDACs). By contrast, a series of PROTACs were identified with high selectivity to the single subtype of PO; for instance, potent and selective CDK9 PROTACs (e.g., THAL–SNS–032) were derived from the nonselective CDK9 inhibitor and exhibited different pharmacological effects to the counterpart inhibitors (Bian et al., 2018; Olson et al., 2018; Robb et al., 2017; Wei et al., 2021). Intriguingly, many reported PROTACs, including several antiviral ones, were also reported to have lower cytotoxicity than those of the corresponding inhibitors (Khan et al., 2019; Niu et al., 2022; Pfaff et al., 2019; Zhang, Thummuri, et al., 2019), although the detailed mechanism of action of the improvement of toxicity have not yet been investigated or determined. In addition, exciting progress has been recently made in circumventing the potential off-target toxicity or side effects of a few PROTAC compounds. In 2020, Reynders et al. published the first application of photo-pharmacology to PROTACs, which incorporated a photo-switchable azo-benzene group into the PROTACs to create PHOtochemically TArgeting Chimeras that target either BET family proteins (BRD2,3,4) or FKBP12, after they were reversibly activated with different wavelengths of light (Reynders et al., 2020). Shi et al. also recently developed a nitroreductase (NTR)-responsive PROTAC prodrug that was synthesized by incorporating the caging group on the VHL ligand and could be activated by NTR to selectively degrade EGFR *in vitro* and *in vivo* (Shi et al., 2022). Similarly, based on NAD(P)H quinone dehydrogenase 1 (NQO1), an enzyme overexpressed in cancer cells, Liang et al. constructed a Pro-PROTAC that could be activated by NQO1 followed by degradation of bromodomain-containing protein 4 (BRD4) with enhanced cell selectivity (Liang et al., 2022).

The application of the PROTAC strategy will certainly accelerate the process of antiviral drug development, we must, nevertheless, acknowledge the inevitable limits. From the perspective of antiviral drug discovery, the PROTAC strategy may face the following bottlenecks.

1) Limitations in understanding of the specific virus. Generally, the discovery of antiviral agents largely relies on both a clear infection mechanism and the structural resolution of viral proteins, and the same is true for the PROTACs. However, the understanding of different viruses remains limited (Katz et al., 2022; Liang & Bushman, 2021), and this may hinder the application prospect of the PROTAC strategy in the field of antivirals. In addition, different viruses are enriched in different host tissues, such as lungs (e.g., influenza virus and coronavirus), liver (e.g., hepatitis virus), and intestines (e.g., enterovirus). The distribution of E3 ligase can significantly differ between different tissue cells (Nieto-Jimenez et al., 2022), potentially significantly affecting the degradation efficiency of antiviral PROTACs containing the same E3 ligand. Similarly, the classes, concentrations, and substrates of E3 ligases vary greatly in various subcellular structures and microenvironments in the cell, and the localization of diverse viral proteins is dynamic during viral replication (Sherman et al., 2020), and thus it would be challenging to selecting an appropriate E3 ligase to induce POI degradation before the detailed structure and infection mechanism of the virus are solved. For example, DCAF16, a nuclear E3 ligase, exclusively promotes the degradation of nuclear proteins (Zhang, Crowley, et al., 2019) however, it might be problematic to recruit this ligase to induce cytoplasmic protein degradation. In addition, certain viral infections may cause lysis of the cell. The depletion effect of PROTACs depends on the intracellular UPS, so currently they are predominantly used to degrade intracellular proteins. However, several viruses infect the host and cause cell lysis, thus damaging the proteasome system, which may ultimately lead to the ineffectiveness of the PROTAC strategy. Therefore, in cases where the degradation function of PROTACs tended to be impaired or lost, the drug combination might be a potential method to exert therapeutic effects. Understanding the structure and physiological functions of viral and host protein targets will therefore considerably benefit the design and application of antiviral PROTACs.
2) Limitations in categories and number of E3 ligands. Although >600 E3 ligases have been discovered and abundant bioactive PROTACs have been developed so far, E3 ligase ligands adapted for PROTAC design are mainly limited to CRBN or VHL ligands (Lee et al., 2022; Sosic et al., 2022). Thus, these PROTACs show restriction due to cell- and tissue-specific expression of E3 ligases. Furthermore, the resistance to several PROTACs containing CRBN or VHL ligands was discovered and reported recently (Ottis et al., 2019; Zhang, Crowley, et al., 2019). Alternatively, administration of drug molecules linked to different E3 ligase ligands has been shown to exhibit different PROTAC efficiencies (De Dominici et al., 2020; Hu et al., 2019) and target selectivity (Anderson et al., 2020) in various cancer cells. The degradation efficiency of degraders involved in cancers and other diseases to exogenous viral proteins is much lower than that of endogenous substrates with micromolar to sub-micromolar DC_{50} values (de Wispelaere et al., 2019; Desantis et al., 2021; Li, Hu, et al., 2022; Xu et al., 2022). Hence, extending the E3 ligand toolbox and finding specific E3 ligases for viral protein degradation will likely increase the success ratio of antiviral PROTACs (Belcher et al., 2021).
3) Limitation in varieties and numbers of antiviral chemical ligands with specific targets. At present, antiviral research is mainly divided into two aspects. One is to design and optimize novel chemical entities for existing targets to obtain inhibitors that are effective against various types of viruses and drug-resistant variants. The second aspect is to find potential targets and develop novel antiviral drugs, which involves long research and development cycles for the discovery of novel antiviral small molecules (Geraghty et al., 2021; Tompa et al., 2021). However, it remains challenging to find compounds that selectively target viral proteins without affecting the normal function of host cells. A series of small-molecule antiviral inhibitors with high potency blocking of virus transmission has been discovered and reported, but for many of them, the mechanism of action is unclear. Moreover, the different subcellular environments of proteins with different POI localizations have been reported to affect the efficacy of PROTAC-mediated degradation (Bekes et al., 2022; Simpson et al., 2022). Thus, the lack of antiviral small-molecule inhibitors partly restricts the discovery of more efficient antiviral degraders.
4) Poor pharmacokinetic (PK) and pharmacodynamic properties. Generally, the molecular weight of PROTACs ranges from 700 to 1200 Da, with more hydrogen bond donors and a larger polar region on the surface than that of traditional small-molecule antivirals, all of which can affect PROTAC cell permeability and oral bioavailability (Han & Sun, 2022). As antiviral PROTACs need to cross the host cell membrane barrier or even the nuclear membrane to exert biological

effects, the transmembrane permeability, becomes a weak point. Moreover, PROTACs hardly conform to the classic rule-of-five by Lipinski (Luo et al., 2021; Testa et al., 2018), causing poor PK properties and low bioavailability in the metabolic process of organisms. Furthermore, the low oral bioavailability due to poor permeability and solubility requires higher doses of oral PROTAC drugs in clinical treatment, potentially causing an increased risk of side effects and manufacturing costs. Thus, the establishment of systematic and credible guidelines to optimize the physicochemical properties and oral bioavailability of antiviral PROTACs is significant for the further study of their druggability.

5) Imperfect preclinical evaluation system of antiviral PROTACs. Compared with the evaluation system of small-molecule inhibitors, antiviral PROTACs need a more precise and stricter control of the POI, and a more in-depth and comprehensive drug safety evaluation system is critical. Moreover, to push antiviral PROTACs into clinical practice in the future, it is vital to establish effective preclinical evaluation systems and databases and reliable experimental models. Nevertheless, the establishment of such evaluation systems is also a time-consuming process that requires significant resources, including labor and material and financial resources.

6. Conclusions and perspectives

The limited targeting of antiviral ligands and the drug resistance generated by frequent mutation of viruses are the two major challenges in the current fight against viral infection (Lozano et al., 2012). Although the application of PROTAC technology in antiviral research has just begun and the number of successful antiviral PROTACs is quite small, these reported PROTAC-based degraders show that they can be used to combat different viruses (e.g., coronavirus and influenza virus) and can effectively overcome viral variants (e.g., HCV NS3–V55A, HCV NS3-A156S, and IAV H274Y) compared with parental inhibitors. Furthermore, the strong catalytic degradation function of anti-IAV PROTAC **V3** (**6**) successfully produced 100% protection for infected mice. However, it is not simple to design an effective antiviral PROTAC molecule at present. The enhancement of the success ratio of antiviral PROTAC design not only calls for expanding the POI and E3 ligand chemical toolboxes but also needs to consider a variety of factors, such as the tissue specificity of viral infection and the localization of viral proteins and E3 ligases in cells. Therefore, the rational design of an antiviral PROTAC molecule should be regarded as an important premise and basis for the development of antiviral degraders. Considering the size and complexity of PROTAC molecules, structure-based drug design strategies will be beneficial to developing antiviral PROTACs, and several studies have established several effective development strategies using *in silico* tools to support the design of PROTACs, including a potent BCL-X_L and BCL-2 (BCL-X_L/2) dual PROTAC that was designed through computational modeling of the entire CRL^{VHL}/PROTAC/BCL-X_L/UbcH5B(E2)-Ub/RBX1 complex (Drummond & Williams, 2019; Ermondi et al., 2021; Weng, Li, et al., 2021). In addition, making full use of existing PROTAC-related databases (e.g., PROTAC-DB database, PROTACpedia database, and DeepPROTACs predictor) (Ermondi et al., 2021; Li, Hu, et al., 2022; Weng, Shen, et al., 2021) to access a variety of information will be helpful in the rational design of antiviral PROTACs.

Finally, click-formed proteolysis targeting chimera, nanocarrier PROTAC (Gao et al., 2022; Yan et al., 2021; Zhang et al., 2021) and antibody-PROTAC conjugate (Ab-PROTAC) (Cotton et al., 2021; Dragovich et al., 2021; Marei et al., 2022) are also potential strategies for effective delivery of active antiviral PROTACs to their targets, with the improvement of physicochemical profiles. Additionally, LYTAC (Banik et al., 2020), AUTAC (Lamark et al., 2017; Levine & Kroemer, 2019), ATEEC (Li, Wang, et al., 2019; Li et al., 2020), MoDE-As (Caianiello et al., 2021), Trim-Away (Clift et al., 2017, 2018; Sui et al., 2021), and CMA (Gómez-Sintes & Arias, 2021; Li, Nie, et al., 2019; Wang et al., 2019) technologies, which are comparable to PROTAC, are also thriving, and it is believed that they will be promising in the antiviral field in the near future.

Author contributions

J.L. and Y.W. wrote the manuscript. K.L., C.D., S.W., S.L., and H.-B.Z. supervised the writing and revision of the manuscripts. All authors have given approval to the final version of the manuscript.

Declaration of competing interest

The authors declare no competing financial interests.

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