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An update on antiviral antibody-based biopharmaceuticals

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ABSTRACT

Due to the vastness of the science virology, it is no longer an offshoot solely of the microbiology. Viruses have become as the causative agents of major epidemics throughout history. Many therapeutic strategies have been used for these microorganisms, and in this way the recognizing of potential targets of viruses is of particular importance for success. For decades, antibodies and antibody fragments have occupied a significant body of the treatment approaches against infectious diseases. Because of their high affinity, they can be designed and engineered against a variety of purposes, mainly since antibody fragments such as scFv, nanobody, diabody, and bispecific antibody have emerged owing to their small size and interesting properties. In this review, we have discussed the antibody discovery and molecular and biological design of antibody fragments as inspiring therapeutic and diagnostic agents against viral targets.

1. Introduction

Viruses are a large, attractive, and diverse group of microorganisms, some of which cause a variety of mild to severe diseases in humans. Human viruses have caused great and deadly diseases and epidemics throughout history in which human beings have a deep history of viral infections. Viruses only grow in living cells and need special receptors on the cells to binding and enter the cell. There have been many and varied efforts to combat these threatening microorganisms and control the human diseases that result from them. Identifying and determining potential targets in pathogenic viruses is an important step in treating the disease. Early and accurate diagnosis, which is dependent highly on viral targets, will certainly help control the disease and its outbreak [1–3].

In spite of the use of many conventional medications, there is still no definitive and effective treatment for most viral infections. Moreover, the emergence of new viruses and their heterogeneity as an alarming rate have evinced that discovery and development of high potent therapeutics is an urgent requirement for the prevention of viral outbreak and epidemics [4,5].

Antibodies are a natural response for neutralizing viruses by either blocking the interaction between the virus and cell host or representing the viral antigens on the cell host to effector cells killing antibody-coated target cells. These cells permit the mechanisms as Antibody-Dependent Cellular Cytotoxicity (ADCC), and Antibody-Dependent Cellular Phagocytosis (ADCP) or a way known as Complement-Dependent Cytotoxicity (CDC) to eliminate infected cells [6]. Monoclonal antibodies (mAbs) owing to the unique properties of target specificity are an important class among therapeutic agents. They have played an unquestionable role in removing the infection [7]. The mAbs neutralize viruses by blocking the interaction between virus and host cell through binding to free virus (opsonization of viruses) or binding to the required receptor on the cell surface for attaching and entering the virus into the cell. They also help to eliminate viral infections by representing the presented antigens on the infected target cell (by opsonization of infected cell) to the immune system effector cells (Fig. 1A). The antibodies bind to the antigens by fragment antigen binding (Fab) and mediate the biological activity by fragment crystallizable (Fc) region, for example, with binding to complement or Fc receptors. Fcγ receptors are expressed on the types of effector cells such as phagocytes, natural killer (NK) cells and dendritic cells. Presentation of infected cells by mAbs to the effector cells leads to mechanisms as ADCC, ADCP

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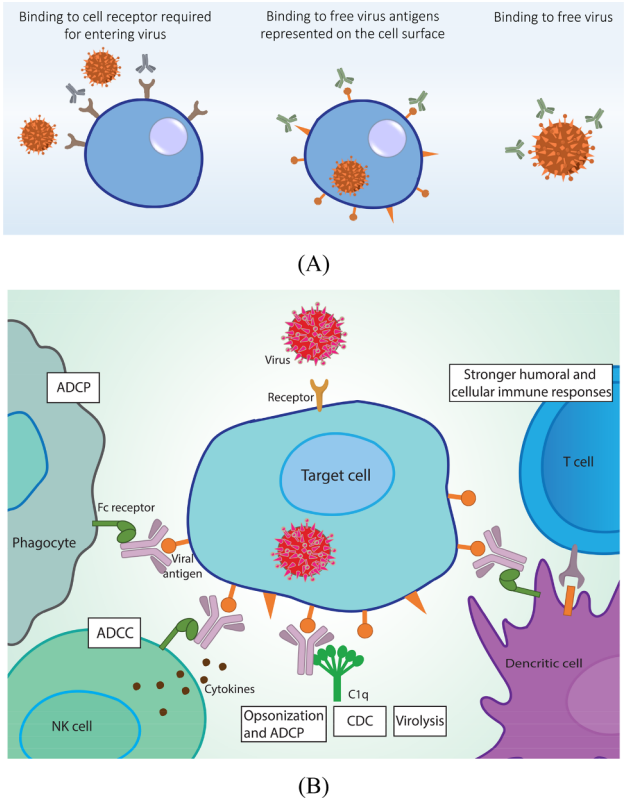

Fig. 1. (A) Ways to neutralize the pathogenic effect of the viruses by mAbs. (B) Fc-mediated activities of antiviral mAbs.

or activation of cellular and humoral cells, CD8 T cells, CD4 T cells and subsequent activation of B cells. Binding to the complement component also may lead to CDC, virolysis or generates virus opsonized. Such viruses opsonized by complement are then eliminated in ways as ADCP (Fig. 1B). The antiviral mAbs that bind to free viruses also can lead to virus elimination through dendritic cells activation, complement activation or ADCP [6,8].

There are few approved therapeutic mAbs for viral infections. Palivizumab and Ibalizumab are two approved monoclonal antibodies for the treatment of human viral infections. However, more therapeutic mAbs are testing in the clinical phases. An antibody-based product, RMAB (Rabishield) that is a single human IgG1 type mAb has been evaluated in a phase II/III clinical trial in India against rabies G glycoprotein. This product was developed for a conformational epitope and could be served as a learning process in designing mAb-based products [9,10]. The mixture of mAbs with different binding potential is also a robust approach for fighting infections in which they have been also developed against viral targets. ZMapp is an antibody mixture (cosfroviximab, larcaviximab, porgaviximab) developed by Mapp Biopharmaceutical, Inc., designed against the Ebola virus glycoprotein in phase II/III clinical trials [11].

Because of highlight in successful targeting and being as inspiring medications, there have been many attempts in recent years to reduce their limitations. These strategies contain engineered antibodies, minimizing strategies and the development of smaller recombinant antibody fragments retaining the targeting specificity of whole mAbs [12]. Although several whole monoclonal antibodies have been approved or are in clinical phases, the use of antibody fragments against viral infections has not yet been approved or entered the clinic. By designing and discovering approaches, maneuvering on the engineering methods and the development of ideal antibody derivatives like single chain variable fragment (scFv), fragment antigen binding (Fab), nanobody or variants like diabody and bispecific antibodies, credible antibody-based biopharmaceutical tools are being developed against the viral targets for diagnosis and treatment applications. More recently, research groups are working to isolate and develop single-domain antibodies (VHHs) from a llama against coronavirus spike. The new coronavirus that currently cause a problematic pandemic named COVID-19 has a large envelope protein called spike for interaction with the host cell. Llama is immunized with this vulnerable target and VHHs are isolated. This VHH-base technology is being used as a rapid detection and treatment of COVID-19 infection [13].

There are some review papers for antiviral mAbs, so this review provides an update on therapeutic and diagnostic potential of mAbs for viral infections. It also explains recent advances on discovery and design of antibodies and then with more focus on antibody derivatives and fragments, especially discuss on credible antiviral biopharmaceuticals based on antibody fragments.

2. Viral targets

Monoclonal antibodies (as highly specific agents), could be used to effectively target pathogens, without disturbing the normal microbiota. Pathogen-specific antibodies that disturb the interaction between a pathogenic protein and the specific host surface receptor (or coreceptor) have shown success in both research and clinic. There are many different viral antigens that due to unique properties can be as potential targets of antibodies. Table 1 represents a summary of the most important viral targets studied.

3. In silico antibody design

Antibodies are the largest class of bio therapeutics, and five monoclonal antibodies are ranked among the top 10 blockbuster drugs. However, their therapeutical usages have faced with some barriers including their complex nature, large size, interaction with the patient immune system, and inadequate pharmacokinetics [30]. The reduction of size to be easily selected and manipulated is the main aim in the production of antibodies. Improving antibody affinity and stability, has been gained through in vitro and in vivo mutagenesis approaches [31]. Antibody engineering aims to produce desirable antibodies through some techniques such as site-directed mutagenesis and random mutagenesis [32,33]. Having simplicity, versatility, rapidness, and cheapness, the error-prone PCR, random mutagenesis methods based on the inaccurate amplification of genes, has been the most common approach for generating libraries. Random mutagenesis and selected mutant library by panning are the parts of this method. To select recombinant antibodies and antibody fragments, with different specificities and affinities from antibody libraries, phage display has been known to be of a great value [34].

Phage display is a potent molecular technique by which peptide or protein of interest is fused to bacteriophage coat proteins and displaying it to the external milieu. It is a reliable source to study protein interactions such as antibody to any antigens and selection the proteins with high affinity for specific targets. There are other display techniques such as ribosome display and mRNA display based on linkage between the gene and the displayed protein by ribosome itself and the physical linkage of a protein to a nucleic acid tag via puromycin, respectively. They all are used to the evolution of proteins to create best ligands with desired properties for binding to the targets. Moreover, as in vitro methods and the high-throughput nature, the conditions of the binding selection are tightly controlled and therefore they are the excellent technological platform to create the antibodies or antibody fragments with enhanced properties by engineering antibody [35–38].

Human IgG1 is the most effective antibody in both CDC and ADCC function and therefore for applications. It is the most appropriate treatment for pathogens or tumor cells. On the other hand, human IgG4 in these two functions is not active and can be used for imaging or blocking molecular intracranial. The Fc region is also associated with

Table 1
Some viral targets of antibodies.

Therapeutic Applications				
Virus	Target	Description	Efficacy of targeting	Ref.
RSV	F surface glycoprotein	This protein carries out an impressive structural rearrangement leading to membrane fusion and plays a key role in RSV infection and pathogenesis.	Inhibition of viral fusion	[14,15]
Human influenza A virus	hemagglutinin protein (HA)			[16]
HIV-1	Host viral receptor-CD4	CD4 molecule contributes to the fusion of cell and viral membranes.	Interferes with the binding of HIV-1 to its primary receptor on target cells and inhibition of HIV-1 Entry to the host cell	[17]
	Host viral receptor-CCR5	CCR5 often acts with CD4 as a co-receptor for the virus.	Inhibition of HIV-1 Entry to the host cell	[18]
	Envelope glycoprotein (Env)	Defined vulnerable epitopes on its surface such as the CD4 binding site and the V3 loop.	Inhibition of the CD4-binding	[19]
	gp120	Mediates attachment of HIV to human CD4 and CCR5 expressing cells.		[20]
	p24	HIV-1 capsid protein p24 plays key roles in HIV pathogenesis.	Inhibition of the replication of HIV-1 in target cells	[21]
HBV	the antigenic loop of HBsAg	Neutralizing viral entry and blocking the interaction with the pre-receptor heparan sulphate proteoglycan (HSPG).		[22]
	The preS1 segment of the large envelope glycoprotein	This segment is essential for virion attachment and infection.	Inhibition of HBV entry to the host cell	[23]
Flaviviruses (such as Zika virus)	Domain III of E protein	The E protein has three domains (DI, DII, and DIII) and domain DIII contains the receptor-binding site.	Inhibition of virus attachment	[24]
Coronaviruses • SARS-CoV • MERS-CoV • SARS-CoV-2	S1 domain of spike glycoprotein	The S1 domain acts as a major antigen on the surface of the virus and has a receptor-binding domain (RBD).	preventing virus attachment to its receptor	[25,26]
Diagnostic applications				
Virus	Target	Description		Ref.
HPV	HPV L1 protein	L1 protein is a major capsid protein of human papillomavirus. Ani-LI antibody can be valuable in detection and clinical screening of cervical cancer. Detection of HPV in cervical exfoliated cells		[27]
Dengue Virus	NS1	Nonstructural protein 1 is secreted from infected cells as a water soluble hexamer form (sNS1) or as a membrane-associated protein (mNS1). Generally, with the onset of symptoms, NS1 appears in the patient's blood and can be detected before IgM antibodies.		[28]
MERS-CoV	Nucleocapsid protein (NP)	N protein functions in viral RNA genome packaging, viral transcription and assembly. NP is present at high levels in infected cells.		[29]

the serum half-life of antibodies, and it can be engineered it to reduce or increase the antibody half-life depending on its application [39]. In addition, in humanized antibodies, only the CDR loops (six loops from the original antibody; three of the heavy chain variables and three of the second light chain variables) are responsible for detecting and binding to the antigen are linked to the second human variable, known as the "graft CDR." To restore the initial affinity of the primary mouse mAbs, the key amino acids of the framework, which maintain the conformation of the CDR loops in the mouse antibody, are also transplanted into the human antibody. Since the first human antibody, Zenapax in 1997 entered the market, seven other humanized antibodies have been used for treatment [40].

Antibody engineering is a very active area for increasing the tendency for binding to the antigens. Regardless of whether an antibody is made by a hybridoma, a phage library, or other technologies, antibodies need to be improved for their affinity to specific antigen. Affinity is not only mechanically important, but also increasing the affinity of an antibody increases its biological activity and improves treatment. It also reduces the dose of antibody therapy and thus reduces toxicity [41].

An example for antibody engineering and affinity improving is about used mAbs against S protein of coronaviruses. Several mAbs have already been represented against SARS-CoV including CR3014, m396, CR3022 and the recently m336 mAb which is a human MERS-CoV-specific monoclonal antibody [42]. The receptor-binding domain (RBD) of the S protein (193 amino acid: N318-V510) is considered as the main target for neutralizing antibodies [43]. Different epitopes on RBD are recognized by various antibodies; for instance, the CR3022 and CR3014 neutralizing antibodies noncompetitively interact with RBD and synergistically neutralize the virus entry into the target cells. Some of the most potent SARS-CoV specific neutralizing antibodies (e.g., CR3014 and m396) failed to show neutralizing effects against SARS-CoV-2. On the other hands, the CR3022 can be a candidate as therapeutic neutralizing antibody against SARS-CoV-2 either in combination with other neutralizing antibodies or alone [44]. Prabakaran *et al.* indicated the interaction of several residues from the heavy chain (33T, 31S, 58A, 52T, and 97A) and from the light chain (96Y) of the m396 antibody with ACE2 antigen. Additionally, Thr33 and Ser31 located in H1 region, Thr52 and Asn58 residues from the H2 region and Val97 located in the H3 region are other residues interacting with the ACE2 antigen. Given these properties, optimization of the m396 properties to enhance its affinity towards the ACE2 protein could be beneficial. Therefore, the introduction of new mutations within the sequence of this antibody is envisaged in which leads to an affinity maturation against the ACE2 from SARS-CoV-2 [45].

4. Diagnostic potential of recombinant antibody fragments

Monoclonal antibodies have gotten progressively acknowledged as diagnostics for different human infections because of their high affinity and specificity [46,47]. With the using of DNA recombinant technology and the development of antibody engendering methods, numerous recombinant antibodies such as Fabs, scFvs, diabodies and single domain antibodies (sdAbs), like VHHs, Shark Variable New Antigen Receptors (V_{NARs}) and variable lymphocyte receptors (VLRs) that include amazing organic exercises were found in camelids, cartilaginous fish and lampreys. These fragments have separately developed. They not only hold the specificity of the entire monoclonal antibodies, but also can be expressed more easily in prokaryotic expression systems [48]. These useful research tools that have revolutionized medicine science are used extensively in diagnosis assays for the detection of various pathogens. They have shown good results in the diagnosis of harmful human viruses.

V_{NAR}, a new immunoglobulin-based protein, observed in sharks are an example with diagnosis application. Unlike traditional mAbs, various benefits of VNARs such as small size, higher thermostability and unusual paratope structure have significantly attracted researchers attention [49]. Feng, M. *et a.l* developed a library production approach to construct a V_{NAR} antibody library. Their method was based on polymerase chain reaction (PCR)-Extension Assembly and Self-Ligation (named "EASeL") to assemble a massive V_{NAR} antibody library. They recognized binders to viral antigens that contained both Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) spike proteins. The isolated shark's single-domain antibodies have been produced in *Escherichia coli* and confirmed for their antigen binding. A Type II VNAR (PE38-B6) showed an excessive affinity (Kd = 10.1 nM) for its antigen [49].

Other antibody derivatives have been considered as potential candidates for success detection of viruses. Doerflinger SY *et al.* established a fast Nanobody-based lateral flow immunoassay (Nano-immunochromatography [Nano-IC]) for the detection of human norovirus in clinical specimens. The Nano-IC technique had 80% and 86% for sensitivity and specificity respectively for outbreak specimens. However, additional adjustments to the Nano-IC technique are needed to enhance this sensitivity, which might also be done via the addition of different widely reactive Nanobodies to the device [50]. In another study, Liu JL *et al.* made a single domain fragment antibody for Ebola virus envelope glycoprotein (GP) and enhanced its solidity to extend its efficiency to use in austere locals. A llama was immunized with killed Ebola virus and GP recombinant protein and an immune phage library containing greater than 10^7 special clones was developed. They isolated three GP binders with a dissociation constants ranging between ~2 to 20 nM and melting temperatures between ~57 to 72 °C. They suggest that future efforts can elucidate the potential of these isolated single domain antibodies as candidates for diagnostic or therapeutic purposes for Ebola [51]. Zhu M. *et al.* have been proposed a sandwich ELISA based on two nanobodies derived from a camel that had been immunized with inactivated semi-purified A/Texas/1/1977 H3N2 virus. These nanobodies had distinctive ability to identify the hemagglutinin of an H3N2 virus. In a sandwich ELISA, in which one of the nanobodies was used to be bound to magnetic beads and the another one was coupled with a reporter enzyme, the semi-purified H3N2 virus was detectable up to a least concentration of 50 ng/mL [52]. In a study, specific useful scFv antibodies were selected against GB virus C (GBV-C) non-structural proteins. GBV-C non-structural proteins were expressed in *E. coli* and a naive scFv library was constructed. These recombinant scFv antibodies may be a precious device for further study of GBV-C and contribute to the progress of a rapid and precise test for identification of GBV-C infection [53].

Antibody fragments would probably illustrate a useful, actual and low cost choice in Ebola diagnostics applications than full-length antibodies. Rodriguez-Martinez LM *et al.* expressed three recombinant anti-GP scfv fragments in *E. coli* cultures. These scFvs contained the heavy and light variable parts of the three well-studied anti-GP full-length mAbs. All three scfvs showed distinctive anti-GP binding activity in ELISA experiments similar to the full sized anti-GP antibodies. It is necessary that the usage of samples containing proper EBOV particles and samples from Ebola disease patients have to be studied to entirely validate the diagnostic usefulness of these scFvs [54].

ScFv antibodies were also developed against ZIKV envelope protein using phage display technology. In this study, after bio-panning, 4 scFvs showed specific binding affinity to ZIKV_E proteins that could be proposed for both diagnostic or therapeutic perspectives for ZIKV [55]. In a different study, Matsunaga S *et al.* designed a novel synNotch receptor including scFv against HBsAg (hepatitis B antigens) linked with an intracellular synthetic transcription factor and suggested it for viral sensing and cellular immunotherapy. The designed system sensed HBV particles and membrane-bound HBs antigens and reacted expressing reporter molecules, secNL or GFP [56]. In another study, Berrin Erdaga KBB *et al.* by using of DNA recombinant technology designed a new anti-HBsAg/Alkaline phosphatase bifunctional scFv for detecting HBsAg. They suggested that their anti-HBsAg scFvs can be used in one-step ELISA after additional linker optimization studies [57].

Bispecific antibodies that are designed for binding to two targets and are being used significantly for different medicinal areas could be also employed as an appealing diagnostic tool for detecting viral targets. Chen YP *et al.* designed a bispecific diabody against human red blood cells (RBCs) and hepatitis B virus antigen (HBsAg) to detect HBsAg in blood samples. In enzyme-linked immunosorbent assays (ELISA), this bispecific diabody showed accurate binding to each RBCs and HBsAg. When the results were compared with those of the traditional immunoassay, as a reference, this diabody-mediated agglutination assay represented a promising result with 97.7% sensitivity and 100% specificity [58].

5. Antibodies fragments as therapeutics against viral infections

Although mAbs currently are one of the effectiveness class of biopharmaceutical, but the use of them in viral therapy has not yet been extensively routine. In absent of viral vaccines, development neutralizing mAbs against various viruses such as H5N1 influenza virus, human immunodeficiency virus (HIV), herpes simplex virus (HSV), cytomegalovirus (CMV), hepatitis C virus (HCV), Ebola virus, Marburg virus, SARS virus, dengue virus, rabies virus, Hendra virus, Nipah virus, yellow fever virus, and West Nile virus have been described in the past few years demonstrating efficacy of mAbs against viral infection [59]. Palivizumab (Synagis) and Ibalizumab (Trogarzo) are two approved monoclonal antibodies against the respiratory syncytial virus (RSV) and HIV, respectively. Table 2 shows the main therapeutic mAbs against the target viral.

Human viruses generate potent, neutralizing antibody responses that can be potent modalities for inhibiting virus infections [67]. Currently, because of discussed challenges in the whole mAb such as large size, high cost of production, low yield, mispairing and complexity in production, antibody fragments have been considered as next generation mAb [68]. Accessibility to viral epitopes is a bottle neck point in the development of antiviral mAb. scFv, Fab, single domain antibody (sdAb) such as camelid VHH are more interesting in antibody engineering for the treatment of viral infections. Phage display is a robust technology for isolation the antibody fragments such as scFv, VHH or other binding oligo peptides. In this way, for a better and more successful treatment, library construction from the infected patient or *in silico* affinity maturation helps to high affinity antibody [69].

ALX-0171 is a trimeric domain Nanobody based-drug that binds the antigenic site II of RSV F protein. ALX-0171 completely inhibited replication under detection rate. The function of ALX-0171 in virus titer removal from nasal and lung is more effective than palivizumab, a humanized monoclonal antibody [70]. Development of VHH based-drug against human immunodeficiency virus-1 (HIV-1) [71], influenza viruses [72], hepatitis C virus (HCV) [73] are ongoing.

VHHs against influenza A virus nucleoprotein (NP) bind to non-conserved region on the body domain of NP and protect cells from viral infection. The antiviral activity of this VHH was shown by blocking the nuclear entry of viral ribonucleoproteins as well as transcription and replication of the viral genome in the nucleus [74].

In addition of VHH, scFv construction against spike protein of porcine epidemic diarrhea virus (from corona virus family) provides a protection against viral infection in piglets [75]. Phoolcharoen *et al.* used a scFv with neutralizing potential on rabies in which was chemically conjugated with RVG (a 29 amino acid peptide) specifically for nicotinic acetylcholine receptor (nAchR) binding in the CNS. The molecule entered neuronal cells more efficiently than scFv suggesting as a novel tool against rabies in the brain [76]. ScFvs derived from immune phage display library against viral-replicon particles expressing the glycoproteins (GP) of marburg virus demonstrated protective efficacies ranging from 75 to 100% in mice that have challenge with wild-type marburg virus [77]

Fragment domain–modified antibodies was developed via insertion two substitution mutations in domains of the highly potent HIV-specific 3BNC117 and 10-1074 bNAbs (broadly neutralizing antibodies) to enhancement half-lives and efficacy for blocking infection following repeated mucosal challenges of rhesus macaques with the simian–HIV [6]. In other study, scFvs of HIV bNAbs designated for clinical testing that target four regions, V2-apex, V3-glycan supersite, CD4 binding site, and MPER (the membrane-proximal external region in the HIV-1 Env gp41 subunit) were expressed. With a variable loss of function compared to IgG but all scFs showed good neutralizing activity indicating antibody fragments suitable for passive immunization to prevent HIV-1 infection [78].

6. Antibody design against cellular targets (curing viral diseases by targeting host)

Although antiviral drugs are designed to target viral proteins and have been successfully developed for curing viral infections, but due to viral resistance there are a narrow spectrum of action and immediate need for replacement. This have forced drug leaders in the industry to look for new drug targets [79]. Recently, a variety of approaches have been developed in diagnosis, treatment and prevention of viral diseases on the basis of neutralization or modification of cellular or molecular targets. Since targeted drugs interact with their targets based on their specificity, antibodies and recombinant proteins are among the best choices. A new generation of potent monoclonal antibodies against viral diseases has been introduced in the past decade. The advancement of technology and the strong desire of scientists to produce new drugs that put different targets together resulted in the development of bispecific antibodies involving two targets in a therapeutic strategy for a specific disease (e.g. viral infections). From two categories of bispecific antibodies, the one that can connect two target cells are considered for treating the viral diseases much more than the others.

In order to prevent Hepatitis C virus infection (HCV), Meuleman *et al.* developed a human IgG4 monoclonal antibody named mAb16-71 that targets scavenger receptor class B type I (SR-BI). This mAb can effectively prevent infection of Huh7.5 cell line and primary hepatocytes of HCV. It inhibits cell to cell transmission of the virus. Efficacy of mAb16-71 was evaluated in uPA-SCID mice by treating 1 day before and 3 days after viral inoculation. Results showed that in 1 day before inoculation, all chimeric mice were protected against different types of HCV genotype and in 3 days after inoculation the viral load was decreased. They revealed that mAb targeting the HCV co-receptor SR-BI prevents intrahepatic viral infection and the spread of different

Table 2
The main therapeutic mAbs against human pathogenic viruses.

Therapeutic	Brand name	Format	Target	Disease/Virus	Status	Ref.
Palivizumab	Synagis, Abbosynagis	Whole antibody	Virus F protein	RSV	Approved	[60]
Ibalizumab	Trogarzo	Whole antibody	CD4 receptor	HIV	Approved	[61]
Motavizumab (MEDI-524)	Numax	Whole antibody	Virus F protein	RSV	Phase II/III-discontinued	[62]
Nirsevimab (MEDI8897)		Whole antibody	Virus F protein	RSV	Phase II	[63]
Sevirumab (MSL-109)	Protovir	Whole antibody	Envelope glycoprotein H	CMV	Phase II	[64]
Leronlimab (PRO140)		Whole antibody	CCR5	HIV	Phase II/III	[65]
Diridavumab (CR6261)		Whole antibody	A Hemagglutinin	Influenza A	Unknown	[66]

genotypes [80].

Zhang *et al.* used a genome-wide CRISPR-Cas9-based screen for identification of a receptor for multiple emerging arthritogenic alphaviruses, including chikungunya, Ross River, Mayaro and O'nyong nyong viruses. They introduced the cell adhesion molecule Mxra8 (Matrix Remodeling Associated 8) as an entry mediator for viral entrance. During their experiments, it was recognized that anti-Mxra8 monoclonal antibody can blocked chikungunya virus infection in different cell types, including primary human synovial fibroblasts, osteoblasts, chondrocytes and skeletal muscle cells. They suggested this mAb as a pharmaceutical target [81].

Fab of 2F4, a mouse monoclonal antibody against the measles virus, prevents viral entry via two cellular receptors, SLAM and Nectin4 with nanomolar affinity range. In addition of 2F4 Fab, scFv prevented the entry of viral particles by blocking receptor binding [82].

Bispecific antibodies are demonstrated that protect human and even animal models from HIV infection. Khan *et al.* designed molecules that cross target both the main HIV co-receptors, CCR5, and Env. These molecules neutralized 98 to 100% of a 109-virus panel. It was designed as tandem single-chain variable fragments (scFvs) (10E8fv-N6fv and m36.4-PRO 140fv), displayed median 50% inhibitory concentration (IC50s) of 0.0685 and 0.0131. A trispecific antibody was also designed contains 10E8-PGT121-PGDM1400 Env-specific binding sites. It has the same potential as the former one (median IC50 of 0.0135 g/ml), while a trispecific molecule 10E8Fab-PGDM1400fv-PRO 140fv can simultaneously target Env and CCR5 with greater potency. They also constructed a trispecific prototype containing reconstituted CH2-CH3 domains restoring Fc receptor binding capacity. All three designed antibodies have shown as efficient tools nad prophylactic and therapeutic agents against HIV [83]. In order to overcome antiviral limitations, Song *et al.* constructed bispecific antibodies (biAbs) using single-chain variable fragments of anti-gp120 bNAbs fused to ibalizumab (iMab), a humanized monoclonal antibody that binds human CD4, the primary receptor for HIV-1. Results showed an improvement of 100% breath [84].

Coronaviruses cause cytokine release syndrome (CRS) with various degrees in severe patients infected with SARS, MERS and newly discovered virus named SARS-CoV-2. A small clinical trial was performed during SARS-CoV-2 in China that showed tocilizumab that have a good efficacy in blocking the signal transduction pathway of inflammatory protein IL-6 played an important role in CRS. In a related study, Xiaoling *et al.* introduce tocilizumab as an effective drug for rescuing patients with SARS-CoV-2 due to the return of the patient's body temperature to normal and an improvement in respiratory functions [85]. In a case report study, Michot *et al.* confirmed that a patient with COVID-19 related respiratory failure can be treated with this drug [86]. In this time, there is a phase III clinical trial of tocilizumab, brand-named Actemra for the treatment of adults with severe COVID-19.

7. Future perspectives

Although there are many therapeutic mAbs for treating different types of diseases on the market, however few therapeutic mAbs are approved as antiviral agents. This can be due to various reasons, but some challenges can be solved with minimizing and engineering the antibodies. So far, there are no antiviral biopharmaceuticals based on antibody fragments, but many efforts being currently concentrated on these types of therapeutics for viral infections, and it is expected that in the near future these products will enter clinical phases and even enter the market and be a significant body of therapeutic agents against infectious diseases especially viral targets.

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