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Review

Antibody Therapy Targeting GP in Treatment of Ebola Virus Infection

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Abstract: Ebola Virus Disease (EVD) is a severe and acute fatal disease caused by the *Orthoebolavirus zairense* (Ebola virus, EBOV), first identified in 1976. From 1976 to 2025, multiple Ebola virus disease outbreaks were documented, predominantly attributable to the Zaire ebolavirus (ZEBOV) species, followed by *Orthoebolavirus sudanense* (Sudan ebolavirus, SUDV), with a limited number of outbreaks associated with *Orthoebolavirus bundibugyoense* (Bundibugyo ebolavirus, BDBV). As of 2025, numerous outbreaks caused by the EBOV have severely impacted public health and the global economy, particularly in West Africa. One of the response strategies has been the development of broad-spectrum neutralizing antibodies for prevention and treatment. ZMapp was the first antibody cocktail authorized for the emergency treatment of patients infected with ZEBOV. To date, two antibody-based therapeutics—Inmazeb and Ebanga—have been officially approved by the FDA in 2020 for the treatment of ZEBOV infection. Following the discovery of these ZEBOV-specific antibodies, numerous antibodies with broader antiviral spectra have been identified and are currently under development. This review summarizes neutralizing antibodies targeting seven key domains of the EBOV glycoprotein (GP), specifically: the glycan cap, GP1/head, base, fusion loop, GP1/core, GP1/2, and HR2/MPER (Heptad Repeat 2/Membrane-Proximal External Region). A deeper understanding of the characteristics of these neutralizing antibodies will accelerate the development of novel antibody therapies and provide guidance for the rational design of next-generation drugs against EBOV infection.

Keywords: ebola virus; neutralizing antibody; glycoprotein

1. Introduction

Ebola Virus (EBOV) belongs to the Filoviridae family and is a single-stranded negative-sense RNA virus that causes severe hemorrhagic fever in humans and other primates. The virus is highly contagious and exhibits an exceptionally high fatality rate, reaching up to 90% in the absence of medical treatment, which renders it one of the most lethal viral diseases (termed Ebola Virus Disease, EVD) in the past two decades [1,2]. Transmission of EBOV occurs through direct contact with the body fluid (such as blood, saliva, sweat, breast milk, semen, and feces) of an infected person or animal during the acute phase of the disease, or by contact with contaminated objects (such as needles, syringes, and clothing) [3]. The virus can enter the body through cuts on the skin or by touching the eyes, nose, or mouth. The Ebola virus is classified into six serotypes: Zaire ebolavirus (ZEBOV), Sudan ebolavirus (SUDV), *Orthoebolavirus restonense* (Reston virus, RESTV), *Orthoebolavirus taiense* (Taï Forest ebolavirus, TAFV), Bundibugyo ebolavirus (BDBV), and *Orthoebolavirus bombaliense* (Bombali ebolavirus, BOMV) [4,5]. The largest Ebola outbreak to date occurred in West Africa during 2014–2016, resulting in more than 28,000 cases and 11,000 deaths [6]. The latest outbreak occurred from 2022 to 2023 and was caused by the SUDV genotype, with 164 reported cases [7]. More recently, in September 2025, the Democratic Republic of the Congo reported an outbreak of Zaire ebolavirus in Bulape Health Zone, Kasai Province—the country's 16th

EVD outbreak [8]. The outbreak resulted in 64 cases and 45 deaths (CFR: 70.3%) before being declared over in December 2025. The virus causes severe clinical symptoms, including fever, fatigue, muscle pain, headache, and sore throat, followed by vomiting, diarrhea, rash, internal bleeding, and external bleeding [9]. The severity of the disease is influenced by various factors, such as the viral strain, viral load, and individual immune responses [10]. The incubation period from infection to symptom onset typically ranges from 2 to 21 days, with the majority of cases occurring within 8 to 10 days [11]. Ebola Virus Disease is only contagious after the onset of symptoms; however, the virus remains transmissible as long as it persists in the body of an infected person even after death.

2. Glycoprotein (GP) of EBOV

The EBOV genome is a linear, non-segmented negative-sense single-stranded RNA of approximately 19 kb, which encodes seven structural proteins through seven genes: the NP (nucleoprotein) gene encoding the nucleoprotein NP, the VP35 (transcriptional activator) gene encoding the polymerase cofactor VP35, the VP40 gene encoding the matrix protein VP40, and the GP gene encoding the glycoprotein GP1/2 and the secreted glycoprotein (sGP). Additionally, several non-structural proteins are also produced [2]. Among these, the GP plays a pivotal role in mediating viral entry into host cells, making it a primary target of paramount importance for the development of antiviral therapeutics.

The Ebola virus GP is a typical class I viral membrane protein. In its native state, GP forms a trimer, with each protomer consisting of a receptor-binding subunit (GP1) and a fusion subunit (GP2) [12]. GP1 and GP2 are interconnected through both disulfide bonds and non-covalent interactions. Viral entry is mediated by the GP, which binds to host cell surface receptors including C-type lectins (e.g., DC-SIGN, Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin) and TIM-1 (T-cell immunoglobulin and mucin domain-containing protein 1) receptors [13–24], thereby facilitating internalization via macropinocytosis [25–27]. Within late endosomes, acidic pH induces conformational changes in GP and proteolytic cleavage by cathepsins, leading to the removal of the mucin-like domain and glycan cap. This processing exposes the receptor-binding site for Niemann-Pick disease type C protein 1 (NPC1) [28–32]. Subsequent binding of GP1 to NPC1 triggers further structural rearrangements in GP2—via a mechanism not yet fully elucidated—that promote fusion between the viral and endosomal membranes, ultimately enabling the release of the viral genome into the host cytoplasm [33–36] (Figure 1).

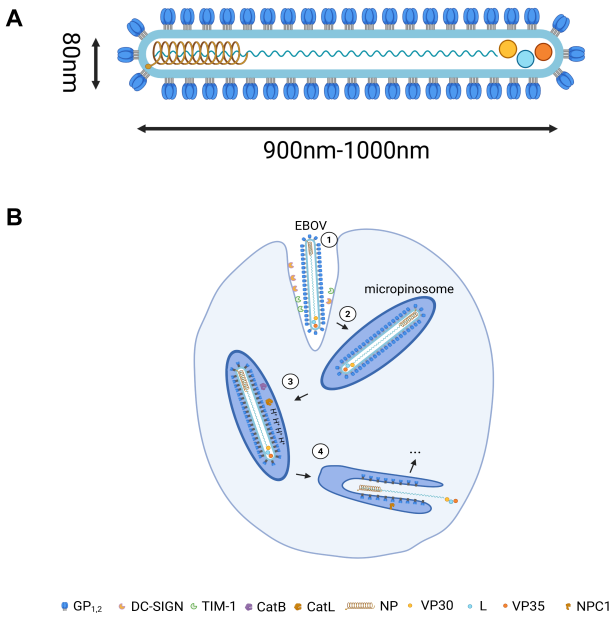

Figure 1. EBOV Genome and Life Cycle. (**A**) Schematic structure of the EBOV particle. (**B**) The attachment of EBOV to host cell surface receptors is mediated by the homotrimeric GP, composed of disulfide-linked GP1 and GP2 subunits. ① The binding to the host cell membrane triggers the endocytosis of the viral particle. ② In the late endosome, GP1/2 is sequentially cleaved by Cathepsin B (CatB) and Cathepsin L (CatL), exposing the receptor-binding site on the GP1 subunit. ③ In the low-pH environment, GP1 interacts with the EBOV receptor NPC1, which then induces a conformational change in GP2, facilitating the fusion of the viral envelope with the endosomal membrane, leading to the release of the ribonucleoprotein complex (mainly composed of RNA and NP) into the cytoplasm. ④ The filovirus genome undergoes replication.

The GP of EBOV serves as the primary target for antibody-based therapeutic development. Since GP, a viral surface protein, is under strong immune selection pressure, considerable sequence variation exists among GP proteins from different EBOV species (Figure 2), presenting a major obstacle for the design of broad-spectrum neutralizing antibodies [37]. Only antibodies targeting conserved critical epitopes are likely to exhibit cross-reactive antiviral activity. Based on antigenic domains, GP can be categorized into several structural regions, including the base, head, glycan cap, mucin-like domain, fusion loop, GP1/core, GP1/2 interface, and HR2/MPER [38] (Figure 2A), among which the head, base, GP1/core, and GP1/2 are spatial epitopes. In terms of amino acid sequence conservation among three different EBOV GP subtypes, the identity is 48% (Figure 2B). Further analysis of amino acid conservation across functional domains of GP reveals distinct patterns: the mucin-like domain demonstrates notably low sequence conservation. This region is primarily involved in shielding immunogenic epitopes and facilitating immune evasion, and is therefore not commonly associated with neutralizing epitopes. In contrast, the fusion loop and HR2/MPER domains exhibit relatively high sequence conservation (Figure 2C). To date, most broad-spectrum neutralizing antibodies against EBOV target the fusion loop epitope. As each domain of GP contributes differently to viral entry and infectivity, antibodies directed against distinct epitopes exhibit varied mechanisms of neutralization.

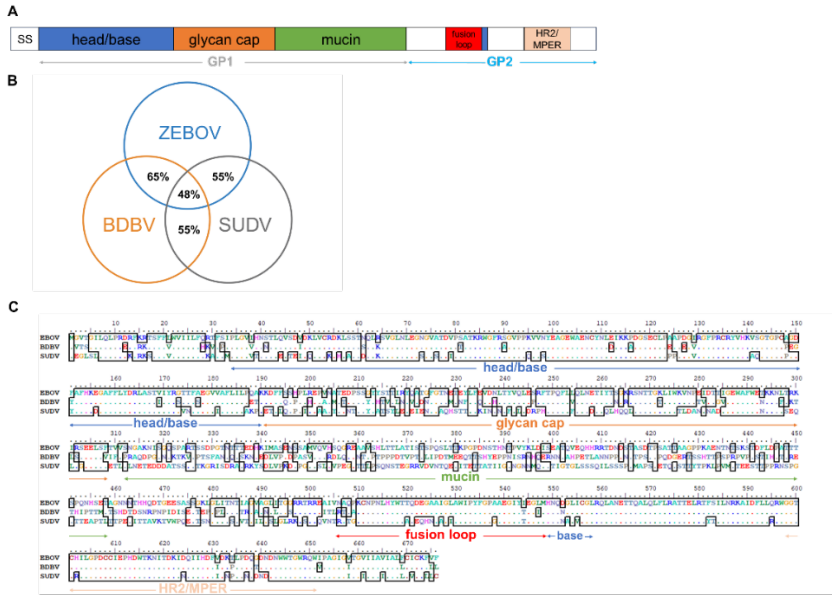

Figure 2. Domain Architecture and Sequence Conservation Analysis of EBOV Glycoprotein. (**A**) Diagram of the GP monomer, colored by domain. The GP is divided into GP1 (34–458) and GP2 (459–676) regions. The GP1 base domain or head domain (34–190, 549–558) is colored blue (because the base domain or head domain is a conformational epitope, it indeed includes residues 549–558 in GP2), the glycan cap domain (191–308) is colored orange, the mucin domain (312–458) is colored green, the internal fusion loop of GP2 (506–547) is colored red, and the HR2/MPER domain (598–651) is colored beige. The remaining domains are uncolored with a signal region. For clarity, the disulfide bonds within and between GP1 and GP2 are omitted. (**B**) Sequence conservation among GP proteins of ZEBOV (Mayinga variant; GenBank: NP_066246.1) (blue), BDBV (Uganda variant; GenBank: YP_003815435.1) (orange), and SUDV (Boniface variant; GenBank: AAB37096.1) (gray). Pairwise sequence identities are as follows: ZEBOV vs. BDBV, 65%; BDBV vs. SUDV, 55%; ZEBOV vs. SUDV, 55%; overall identity across all three viruses, 48%. (**C**) Domain-specific sequence conservation analysis of ZEBOV, BDBV, and SUDV GP. Regions within black rectangles indicate segments of BDBV and SUDV GP sequences that are identical to ZEBOV GP.

3. Antibodies Targeting the GP

As one of the most virulent and globally concerning pathogens, EBOV remains a major focus and ongoing challenge in virology research. Considerable efforts have been dedicated to the development and characterization of monoclonal antibodies (mAbs) against EBOV, leading to the identification of hundreds of antibodies with diverse biochemical and functional properties. These mAbs differ widely in origin, epitope specificity, and neutralization potency, which collectively influence their breadth of reactivity across ebolavirus species and protective efficacy *in vivo*. Table 1 summarizes a selection of monoclonal antibodies targeting EBOV GP, including their origins, epitope classifications, neutralization profiles, cross-reactivity among ebolaviruses, and *in vivo* protective performance in animal models.

Table 1. Summary of selected monoclonal antibodies targeting the EBOV GP.

Name	Epitope	Breadth	Neutralization ($IC50$)	*In Vivo* Protective Efficacy	Ref.
ZMapp™ (c13C6, c2G4, c4G7)	glycan cap, base, and base respectively	ZEBOV	UD	Rhesus macaques with 50 mg/kg of ZMapp™ at 3, 6 and 9 dpi (days post infection); 4, 7, and 10 dpi; or 5, 8 and 11 dpi (100% survived)	[39]
mAb114	Head	ZEBOV	The $IC50$ for lentivirus particles of pseudotype EBOV GP is 6 nM	Macaques with 50 mg/kg of mAb114 at 1, 2 and 3 dpi (3 animals, 100% survived)	[40]
CA45	Fusion loop	ZEBOV, BDBV, SUDV	28.3 nM, 78.2 nM and 5.5 nM for ZEBOV, SUDV and BDBV respectively	BALB/c mice were infected with mouse-adapted ZEBOV followed by intraperitoneal (i.p.) injection of 2.5 mg/kg CA45,2 (dpi) (20 animals, 95% survived); SUDV model (mice) by using mice deficient for the IFNa receptor (B6.129S2-Ifnar1tm1Agt/Mmjax) were challenged with SUDV (1000 $p.f.u.$) and treated by a single i.p. injection of mAbs at 1 dpi. CA45 (10 mg/kg) protected five out of six animals from lethal infection (6 animals, 83% survived); Guinea pigs infected with 1000 $LD50$ of guinea-pig-adapted ZEBOV (GPA-ZEBOV) were treated with CA45 at 5 mg/animal (3 dpi, 50% survived); Guinea pigs infected with guinea-pig-adapted SUDV (GPA-SUDV) were treated with CA45 at 5 mg/animal (3 dpi, 100% survived)	[41]
REGN3470, REGN3471 and REGN3479	Glycan cap, head, fusion loop respectively	ZEBOV	$IC50$ of REGN3470 is 0.27 nM; $IC50$ of REGN3471 is 0.17 nM; $IC50$ of REGN3479 is over 20 nM (lentiviral particles pseudotyped with Makona strain EBOV GP)	Rhesus macaque with 2 doses of 50 mg/kg of the antibody mixture (1:1:1) on days 5 and 8 postinfection (5 animals, 100% survived)	[42]
BDBV223	HR2/MPER	ZEBOV, BDBV	$IC50$ for EBOV live virus is about 7 nM; $IC50$ for BDBV live virus is about 0.003 nM	BALB/c female mice (Charles River Laboratories) injected with 1000 $p.f.u.$ (Plaque-forming unit) of the mouse-adapted ZEBOV, strain Mayinga were treated with BDBV223 at 100 μg/animal (1 dpi, 5 animals, 100% survived); ferret infected with BDBV were treated with BDBV223 at 20 mg/animal (3 dpi and 6 dpi, 4 animals, 50% survived)	[43]
rEBOV-442 and rEBOV-515	Glycan cap and base respectively	ZEBOV, BDBV, SUDV	$IC50$ of rEBOV-442 for EBOV live virus is about 6 nM, for BDBV live virus is about 3 nM, for SUDV live virus is about 50 nM; $IC50$ of rEBOV-515 for EBOV live virus is about 3 nM, for BDBV live virus is about 2 nM, for SUDV live virus is about 5 nM	Rhesus macaques were inoculated with a lethal dose of the ZEBOV/Kikwit or SUDV/Gulu via i.m. (Intramuscular administration) on day 0 and were treated with total 30 mg/kg of the cocktail (1:2 mixture of rEBOV-442 and rEBOV-515) intravenously on 3 and 6 dpi (ZEBOV/Kikwit; 5 animals per cohort), or 4 and 7 dpi (SUDV/Gulu; 5 animals per cohort). Cynomolgus monkeys were inoculated with a lethal dose of the BDBV/Uganda via i.m. on day 0 and were treated with a total dose of 30 mg/kg of the cocktail (1:2 mixture of rEBOV-442 and rEBOV-515) intravenously on 6 and 9 dpi (5 animals per cohort) (all 100% survived)	[44]
1C3 and 1C11	chalice bowl; fusion loop	ZEBOV, BDBV, SUDV	$IC50$ of 1C3 for EBOV live virus is about 0.6 nM, for SUDV live virus is about 0.6 nM; $IC50$ of 1C11 for EBOV live virus is about 0.2 nM, for BDBV live virus is about 0.6 nM, for SUDV live virus is about 0.2 nM	Cynomolgus macaques were inoculated with a lethal dose of the ZEBOV via i.m. on day 0 and were treated with total 25 mg/kg of the cocktail (1:1 mixture of 1C3 and 1C11) intravenously on 4 and 7 dpi (3 animals, 100% survived); cynomolgus macaques were inoculated with a lethal dose of the SUDV (Gulu variant) via i.m. on day 0 and were treated with total 50 mg/kg of the cocktail (1:1 mixture of 1C3 and 1C11) intravenously on 4 and 7 dpi (3 animals, 100% survived); STAT-1 (Signal transducer and activator of transcription 1) knockout mice were exposed to 1000 $p.f.u.$ of BDBV-GP via i.p. and treated 24 h later with 0.5 mg 1C3/1C11 cocktail (0.25 mg each; 0.5 mg total) (5 animals, 100% survived)	[45]

3.1. Antibodies Targeting the Base of GP

The base domain of GP is situated within the GP1 and GP2 subunits. Several studies indicate that the GP1/core and GP1/2 regions are largely synonymous with the base domain [20,46–49]. Notable antibodies targeting this domain include rEBOV-515 [44], ADI-15946 [50], KZ52, and the ZMapp [39] cocktail therapy, including 2G4 and 4G7. Among these, rEBOV-515 and ADI-15946 exhibit broader neutralizing breadth compared to KZ52 [20], 2G4, 4G7, and REGN3479. Specifically, while KZ52, 2G4, 4G7, and REGN3479 are specific to EBOV, rEBOV-515 demonstrates neutralizing activity against EBOV, BDBV, and SUDV. ADI-15946 also neutralizes EBOV and BDBV, and exhibits weak neutralization against SUDV pseudovirus.

Epitope mapping reveals that both rEBOV-515 and ADI-15946 primarily target the 3^{10} pocket of the Ebola GP [51]. The key binding sites for rEBOV-515 include E106, R136, K510, C511, N512, H516, H549, and N550, whereas ADI-15946 engages F290, W291, E292, K510, C511, and C556. These residues are highly conserved among diverse EBOV species. Mechanistically, binding of rEBOV-515 and ADI-15946 to the 3^{10} pocket mimics the hydrophobic interactions typically mediated by the β17–β18 loop in the proteolytically cleaved form of GP (GPCL), which is generated upon removal of the mucin and glycan cap by cathepsin B and L to expose the receptor-binding site (RBS). This interaction impedes the rearrangement of GP1 residues 71–75 during GPCL–NPC1 engagement. Furthermore, ADI-15946 is proposed to span the fusion loop, thereby stabilizing the GP1–GP2 interface and preventing conformational changes essential for membrane fusion, including the structural reorganization of the GP1 core during fusion triggering. In contrast, KZ52 recognizes residues V42, L43, Q508, C511, N550, D552, G553, and C556; 2G4 binds primarily to C511, N550, G553, and C556; and 4G7 interacts with C511, D552, and C556. These binding epitopes are not fully conserved across EBOV GP variants, likely explaining the limited breadth of neutralization observed with these antibodies (Figure 3).

Although the critical binding residues for these five antibodies exhibit minor variations, they are generally clustered within the same structural domain. Notably, C511 serves as a common binding site across all five antibodies, underscoring its functional importance in GP activity. These antibodies share a common mechanism of neutralization: they inhibit structural rearrangements within the GP2 HR1A and HR1B domains and prevent the insertion of the internal fusion loop into the host membrane, thereby blocking membrane fusion [49,52]. Despite this shared mechanism, KZ52—for reasons that remain incompletely elucidated—fails to confer protection against live EBOV challenge in non-human primates [53].

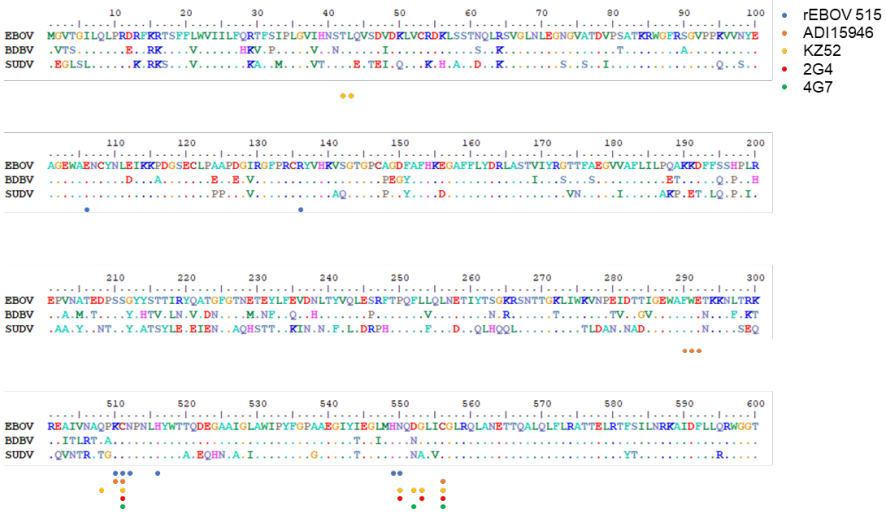

Figure 3. Comparison of binding sites for rEBOV-515, ADI-15946, KZ52, 2G4, and 4G7 on GP. Binding residues are indicated as follows: rEBOV-515 (blue), ADI-15946 (orange), KZ52 (yellow), 2G4 (red), and 4G7 (green). The structure illustrates the location and overlap of epitopes within the GP base domain.

3.2. Antibodies Targeting the Head Domain of GP

Owing to its distal location relative to the viral membrane, the head domain of EBOV GP is highly accessible for antigen presentation. This region represents a major epitope eliciting potent antibody-dependent cellular cytotoxicity (ADCC) [38]. Two FDA-approved therapeutic antibodies, mAb114 [40,54] (a monotherapy) and REGN3471 [42,55] (a key component of the Inmazeb cocktail), primarily target the head domain of EBOV GP, which encompasses the receptor-binding site (RBS). These antibodies mainly function by binding to the RBS

domain on GPCL, thereby blocking interaction with the host receptor NPC1. This inhibition prevents subsequent conformational changes in GP required for membrane fusion.

Among these, mAb114 penetrates the glycan cap and mucin domain barrier by binding to the GPCL core at a nearly vertical angle (approximately 85° relative to the viral membrane), thereby accessing the conserved GP1 internal core. This antibody is capable of recognizing both full-length GP and GPCL, a property believed to underlie its significant efficacy in reducing EBOV mortality to approximately 35% in clinical trials [56]. In contrast, REGN3471 engages an epitope comprising 60% head domain and 40% glycan cap residues. When administered alone, REGN3471 confers partial protection in guinea pigs (33% survival), likely mediated through dual mechanisms of receptor binding inhibition and Fc-mediated effector functions [55].

Additionally, the head domain-targeting antibody 1C3 binds an epitope that spans three protomers within the conserved receptor-binding cleft ("holy grail") and partially overlaps with the NPC1 binding site on GP. This newly identified epitope sterically hinders GP–NPC1 interaction, thereby inhibiting viral entry [45].

3.3. Antibodies Targeting the Glycan Cap Domain of GP

The glycan cap is primarily located on GP1 and contains five N-linked glycosylation sites [14]. These glycans facilitate host cell attachment by interacting with C-type lectins, including DC-SIGN and L-SIGN (Liver/Lymph Node-Specific Intercellular Adhesion Molecule-3 Grabbing Non-Integrin) [18,57,58], and contribute to immune evasion by shielding GP from neutralizing antibodies [59–65]. In current structural studies of EBOV GP, glycan-deficient mutants—such as those incorporating T42V and T230V substitutions—are commonly employed to reduce glycan heterogeneity, enhance structural uniformity, minimize background interference, and improve overall resolution [20].

Antibodies targeting the glycan cap include 13C6 (a component of the ZMapp cocktail), REGN3470 [42,56] (one of the key components of the Inmazeb cocktail), and rEBOV-442 [44]. In addition to their own neutralizing mechanisms against the virus, these antibodies exhibit other independent virus-neutralizing mechanisms mediated by the Fc domain, including antibody-dependent cellular phagocytosis (ADCP), activation of natural killer (NK) cells [38,66], and protection of infected animals via complement system activation [67]. However, monotherapy with glycan cap-targeting antibodies often fails to confer complete protection against EBOV infection *in vivo*. Consequently, they are frequently administered in combination with antibodies directed against other epitopes to synergistically enhance therapeutic efficacy and improve survival outcomes in infected animals [39,42,44,68,69].

3.4. Antibodies Targeting the Mucin Domain of GP

The mucin domain critically contributes to immune evasion by shielding GP from neutralizing antibodies. This domain contains eight N-linked glycosylation sites, along with O-linked and C-linked glycosylation sites, forming a complex and heterogeneous glycan shield. The substantial heterogeneity of these glycans results in a highly variable surface architecture presented to the immune system, thereby diminishing the binding efficiency of antibodies. This reduction occurs in part because many antibody epitopes incorporate glycan residues, and effective neutralizing agents must target conserved core elements within the glycan structure—elements that are subject to considerable variability. Thus, glycans not only sterically hinder access to neutralizing epitopes but also obscure antigenic features of the envelope GP, facilitating immune evasion.

Moreover, the sequence of the mucin domain is highly non-conserved among different EBOV strains (Figure 2C). Consequently, the few conserved amino acid residues within this domain are hypothesized to play essential structural roles in maintaining GP integrity. Antibodies such as 14G7 and 13F6-1-2 target the mucin domain. Although these antibodies do not neutralize the virus very effectively, they confer protection in lethal EBOV challenge mouse models, which is believed to be the result of the Fc-mediated effector functions of the antibodies [68,70].

Despite the extensive glycosylation in the mucin domain, antibodies such as 14G7 and 13F6-1-2 specifically recognize epitopes that are not glycosylated, which is one of the characteristics of protective antibodies targeting the mucin domain of Ebola GP. Due to the high variability in the primary structure of the mucin domain, antibodies directed against this region typically exhibit limited cross-reactive neutralization across diverse EBOV species. Consequently, their utility as broad-spectrum therapeutics may be constrained.

3.5. Antibodies Targeting the Fusion Loop

The fusion loop domain of the GP protein is essential for viral entry. After receiving conformational signals from the GP protein, the fusion loop inserts into the host cell membrane, facilitating the apposition of the viral and cellular membranes. This close proximity catalyzes membrane fusion, thereby completing the viral infection cycle.

Antibodies targeting the fusion loop include CA45, 1C11, REGN3479 (from the Inmazeb cocktail), and ADI15878 (from MBP) [71]. These antibodies function primarily by binding to the GP fusion loop and inhibiting the conformational changes in the GP protein required for the fusion peptide, thus preventing the fusion of the viral membrane with the host cell membrane. The functional importance of the fusion loop is reflected in its high sequence conservation across Ebolavirus species. Consequently, antibodies directed against this region often exhibit broad neutralizing activity. Moreover, by directly disrupting a key step in viral entry, fusion loop-targeting antibodies constitute a highly effective class of antivirals with potent neutralization capacity.

Owing to the central role of the fusion loop in viral membrane fusion, antibodies targeting this domain demonstrate potent neutralizing activity and confer robust protection in animal models. For instance, in a mouse model challenged with EBOV (100 $p.f.u.$), a single intraperitoneal dose of CA45 (2.5 $\mathrm{mg/kg}$) administered at 2 days post-infection protected 19 out of 20 animals from lethal outcome. Similarly, CA45 (10 $\mathrm{mg/kg}$) given at 1 dpi protected 5 out of 6 mice against a lethal challenge with SUDV (1000 $p.f.u.$), demonstrating its efficacy across different ebolavirus species [41].

3.6. Antibodies Targeting HR2/MPER

The HR2/MPER domain is essential for the EBOV GP-mediated membrane fusion process. Within this region, the amino acid residues W645 and W648 play a pivotal role in facilitating the interaction between the fusion loop and MPER, thereby promoting fusion of the viral and host membranes during entry [72]. These tryptophan residues help anchor the fusion loop and MPER at the membrane interface, stabilizing their association and ultimately driving the membrane fusion process required for EBOV infection.

The HR2/MPER domain of EBOV GP represents a recently identified target for neutralizing antibodies. The first neutralizing antibodies discovered against this epitope were BDBV223, BDBV317, and BDBV340 [43]. Subsequent studies have identified additional antibodies targeting this region, including ADI16061 [73], BDBV270, BDBV289, and BDBV324 [74]. Among these, BDBV289 exhibits superior neutralizing potency compared to BDBV270 and BDBV324. Furthermore, BDBV289 has demonstrated protective efficacy in mouse, guinea pig, and rhesus monkeys in EBOV infection models [74,75].

The mechanism of action of these antibodies involves disrupting the interaction between the MPER and fusion loop domains, thereby inhibiting virus-host membrane fusion. Furthermore, antibodies targeting this domain tend to exhibit broad-spectrum neutralizing activity, capable of neutralizing various EBOV strains and providing varying degrees of protection against infections with different EBOV strains in animal models.

Based on these findings, we conducted a systematic evaluation of distinct epitopes on the EBOV GP. This assessment included a comprehensive comparison of antibodies in terms of screening characteristics, protective efficacy, antibody-dependent cellular cytotoxicity (ADCC) activity, neutralization potency, breadth of cross-reactivity, and *in vivo* protective performance (Table 2). In addition, we selected several representative antibodies to summarize the relationship between their neutralizing capacity and neutralization breadth (Figure 4).

Table 2. Functional Evaluation of Antibody Epitopes on EBOV GP. This table systematically compares antibodies directed against various epitopes of the Ebola virus GP, evaluating key parameters such as: the quality and frequency of antibody discovery through screening, protective efficacy, antibody-dependent cellular cytotoxicity (ADCC) activity, neutralization potency, breadth of cross-reactivity across ebolavirus species, and *in vivo* protective performance. Superscripts denote the primary mechanism of action: ^{N} (neutralization), ^{F} (Fc effector functions), or ^{N}&^{F} (both).

Epitope Region	Representative mAbs	Screening Feasibility	Neutralization	ADCC Activity	Breadth	*In Vivo* Protection	Summary
Base	KZ52^{N}, rEBOV-515^{N}, c2G4^{N}, c4G7^{N}	Moderate to high (structure-guided)	Strong	Weak	Poor (A few antibodies that bind to conservative amino acids have good broad spectrum properties)	Robust protection in rodents & NHPs	Weakly conserved; core of many broad therapeutic cocktails
Head	REGN3471$^{N\&F}$, mAb114$^{N\&F}$	Moderate	Strong	Strong	EBOV-specific (±weak BDBV)	Clinical and preclinical efficacy	Target of classical neutralizing antibodies; accessible after cleavage
Glycan cap	13C6$^{N\&F}$, rEBOV-442$^{N\&F}$, REGN3470$^{N\&F}$	High	Weak to moderate	Strong	Poor (A few antibodies that bind to conservative amino acids have good broad spectrum properties)	Partial (Fc-effector dependent)	Commonly targeted; useful for ADCC-based protection in cocktail
Mucin-like-domain (MLD)	14G7^{F}, 13F6-1-2^{F}	High	None	Moderate to strong	Poor	Limited (Fc-effector dependent)	Highly variable; dispensable for viral entry; not ideal vaccine/therapy target
Fusion loop	CA45^{N}, 1C11^{N}, REGN3479^{N}	Structure-dependent	Strong	Weak	Broadly reactive	Strong (in combination)	Recognized after conformational change; targets viral fusion machinery
HR2/MPER	BDBV223^{N}	Technically challenging	Moderate to strong	Weak	BDBV-specific (±weak EBOV)	Partial	Membrane-proximal site; useful in pan-ebolavirus strategies

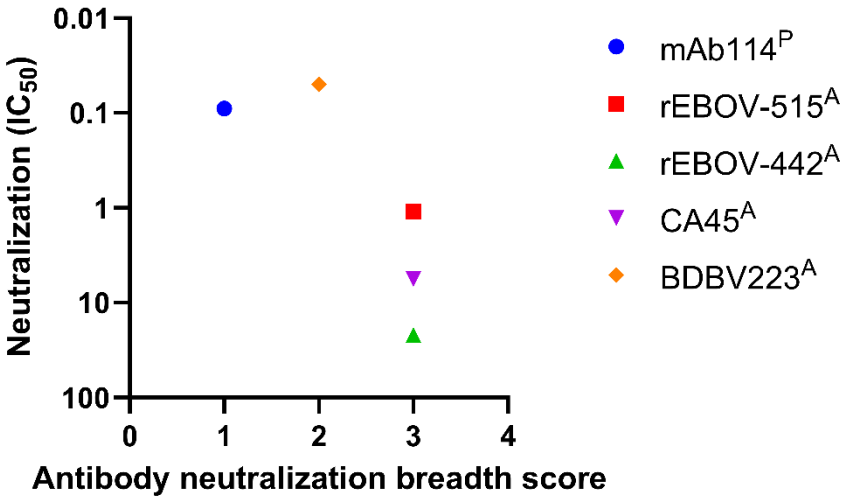

Figure 4. Relationship between Neutralization Potency and Breadth of Representative Antibodies. Neutralization potency (*y*-axis) is shown as the mean IC_{50} (μg/mL) when tested against two or more EBOV viruses. Data points are annotated: A (authentic virus) or P (pseudovirus); values for antibodies neutralizing multiple subtypes are geometric means. Neutralization breadth (*x*-axis) is scored as the number of EBOV subtypes neutralized (1 point per subtype).

3.7. AI-Driven Antibody Design for Ebola Virus

Hastie et al. first employed computational prediction and high-throughput screening to identify the highly conserved and functionally critical stalk–MPER region on the Ebola virus glycoprotein (GP) [75,76]. They subsequently determined the high-resolution structure of the monoclonal antibody 3A6 in complex with this epitope, revealing a "conformational lift" mechanism whereby the antibody displaces the viral surface protein from the membrane environment, thereby blocking membrane fusion. Building on this, they combined dynamic simulations (AlphaFold2/3) and cryo-electron tomography to validate the biophysical feasibility of this mechanism. Ultimately, animal studies confirmed the potent efficacy of this design, even at very low doses against late-stage infection with high viral loads. This work exemplifies a closed-loop, AI-augmented design pipeline—from target identification and mechanistic elucidation to therapeutic validation—providing a transferable framework for the rational design of next-generation broad-spectrum antiviral drugs and vaccines [76].

3.8. Synergistic Antibodies for Ebola Therapy

Synergistic interactions between antibodies are well-established and play a pivotal role in enhancing viral neutralization. This is exemplified by several innovative strategies across different virus families. Wec et al. developed an innovative "Trojan horse" bispecific antibody strategy, synergizing two antibodies to achieve broad neutralization and protection against multiple ebolaviruses [77]. Individually, neither antibody neutralizes the virus: FVM09 acts as the "delivery" vehicle, transporting the bispecific construct into the cell, while mAb-548 or MR72 serves as the "blocker," intracellularly inhibiting viral receptor binding. The resulting Dual-variable domain immunoglobulin (DVD-Ig) demonstrated broad neutralizing capacity against five ebolaviruses (ZEBOV, BDBV, SUDV, TAFV, RESTV). This "Trojan horse" approach not only offers a novel therapeutic avenue for Ebola but also provides a potential platform for other viruses using intracellular receptors, such as Lassa virus. Gilchuk et al. discovered that the antibody pair rEBOV-442/515 exhibits potent synergistic neutralization against three ebolavirus species (EBOV, BDBV, SUDV), with a particularly significant effect against SUDV [44]. This combination demonstrates bidirectional synergistic enhancement upon binding the viral glycoprotein (GP), mutually increasing each other's binding affinity without inducing major conformational changes in GP, likely through stabilization. Furthermore, the combination benefits from complementary mechanisms: rEBOV-515 provides potent neutralization, while rEBOV-442 contributes significant Fc-mediated effector functions, leading to superior *in vivo* protection.

Antibody synergy is a cornerstone strategy for enhancing antiviral therapeutics. It operates through diverse mechanisms—including division of labor (e.g., Trojan horse), order-dependent binding, bidirectional enhancement, and multi-antibody cooperation inducing conformational disruption—to achieve broad-spectrum neutralization, enhance

potency, and overcome viral escape. Future development will leverage these principles to construct more resilient, escape-resistant therapeutic regimes against rapidly evolving RNA viruses. Advances in multispecific antibodies and intelligent cross-linking designs will underpin the next generation of antiviral biologics, offering a reliable path to address viral evolution and laying a solid theoretical and technical foundation for future drug development.

3.9. mRNA Delivery of Antibodies for Ebola

mRNA delivery technology fundamentally circumvents the pharmacokinetic limitations of traditional passively infused monoclonal antibodies—such as finite half-life, inadequate tissue penetration, and the need for high-dose repeated administrations—by transforming human cells into "bioreactors" for the sustained production of functional antibodies. This represents a revolutionary strategy for combating the Ebola virus. The field has recently achieved breakthrough preclinical progress: Fan et al. designed an efficient mRNA framework encoding the pan-ebolavirus broad-spectrum neutralizing antibody 2G1 [78]. Delivered via lipid nanoparticles (LNPs), this construct reached peak expression in mice within 24 h. Notably, its neutralization potency against Ebola and Sudan virus pseudotypes was 19.8-fold and 12.5-fold higher, respectively, than that of its traditional recombinant IgG counterpart, demonstrating the tremendous potential for "single-dose, sustained-effect" prophylaxis or therapy. Leveraging its rapid, flexible, and efficient platform characteristics, mRNA technology holds immense promise for public health responses. It enables vaccine design within weeks based on pathogen genetic sequences, allowing for a swift countermeasure against emerging outbreaks. Its rapid induction of immune responses provides a critical window for post-exposure prophylaxis against diseases like Ebola. Furthermore, advances in delivery systems and formulation are continuously improving the stability and thermostability of mRNA vaccines. Coupled with their scalable manufacturing capacity, this technology promises to overcome the cold-chain dependence and production bottlenecks of traditional vaccines, thereby enabling more equitable and timely access in resource-limited settings. Ultimately, it transforms vaccines from a "pre-stocked commodity" into a rapidly deployable "on-demand medical countermeasure". However, attention must be paid to its potential for undesirably strong immunogenicity [79].

4. Molecular Characteristics and Functional Mechanisms of sGP

4.1. Molecular Characteristics and Generation of sGP

EBOV has been extensively investigated across multiple biological dimensions. With respect to GP gene expression, studies have shown that during transcription, the viral RNA-dependent RNA polymerase undergoes transcriptional stuttering at a heptauridine tract situated upstream of the sGP stop codon. This transcriptional stuttering leads to the insertion of a non-templated adenosine residue, resulting in a frameshift that alters the position of the stop codon [80]. Approximately 25% of the GP gene transcripts are longer mRNAs that encode the GP1/2 precursor. Frameshift mutations arising from the insertion of two adenosines or the deletion of one adenosine produce shorter transcripts that encode a small soluble glycoprotein (ssGP). Specifically, the sGP transcript contains a sequence of seven adenosines (7A), the GP1/2 transcript contains eight adenosines (8A), and the ssGP transcript contains either six or nine adenosines (6A/9A) [81]. sGP forms a homodimer, the stability of which is likely mediated by a hydrophobic interface and interchain disulfide bonds—specifically, Cys53–Cys53 in Loop 1 and Cys306–Cys306 in Loop 3 of the sGP structure [81].

4.2. sGP Serves as a Decoy Antigen

Due to transcriptional frameshifting during GP gene expression, the sGP shares the N-terminal 295 amino acids with the full-length GP, while possesses a unique C-terminal 77-amino-acid sequence. The N-terminal 295 residues of GP encompass portions of the base, head, and glycan cap domains, which represent immunodominant regions of the entire GP protein. Consequently, sGP and GP exhibit a degree of immunological cross-reactivity. sGP has been demonstrated to function as a decoy antigen by binding antibodies specific to GP1/2, potentially facilitating antigenic escape and promoting systemic viral dissemination within the host.

sGP is present at high concentrations in patient sera (~100 μg/mL), which is thought to divert the host humoral immune response away from GP1/2 toward sGP. This phenomenon is supported by data showing that sGP can effectively compete with GP1/2-specific antibodies elicited in sGP-immunized mice [82]. Moreover, sGP interferes with the neutralizing activity of antisera from mice immunized with either GP1/2 or sGP [82].

Conversely, a separate study demonstrated that intradermal or intramuscular vaccination with an adjuvanted sGP subunit vaccine conferred effective protection against lethal EBOV challenge in mice by eliciting antibodies that neutralize both sGP and GP1/2 [83]. sGP induces cross-reactive antibodies recognizing both sGP and GP1/2, suggesting that neutralization of sGP itself may confer therapeutic benefit. Indeed, analysis of multiple cross-

reactive antibodies targeting sGP/GP1/2 demonstrated that some antibodies exhibited superior neutralization of wild-type EBOV expressing sGP compared to VSV pseudoviruses expressing EBOV GP alone (which do not express sGP) [38].

Therefore, the interaction between sGP and antibodies *in vivo* is likely multifaceted. For antibodies capable of cross-neutralizing sGP and GP1/2, sGP may impede viral neutralization by acting as a decoy antigen. Conversely, for other cross-neutralizing antibodies, neutralization of sGP may enhance therapeutic efficacy, as exemplified by the 13C6 antibody in the ZMapp cocktail. Nonetheless, this hypothesis remains contentious, and further investigation is warranted to elucidate the complex role of sGP in antibody-mediated immunity.

4.3. Potential Anti-Inflammatory Role of sGP

Furthermore, emerging evidence suggests that sGP may exhibit anti-inflammatory properties [84]. It is well established that upon EBOV infection, the virus initially targets components of the host immune system, including macrophages, dendritic cells, and lymphocytes [85]. Kindzelskii et al. demonstrated that sGP significantly reduces the expression of the CD16b receptor on human neutrophils in a dose-dependent manner [86]. They also found that sGP induces conformational changes in this receptor, thereby inhibiting neutrophil activation and blocking innate immune responses by preventing immune complex–mediated neutrophil activation.

Indeed, during EBOV infection, many focal tissue lesions in organs such as the liver and kidneys exhibit an absence of leukocyte infiltration despite prominent neutrophil accumulation within the vasculature [84]. This phenomenon may be attributed to sGP-induced restoration of endothelial barrier function, which suppresses leukocyte transmigration across the endothelium. Wahl-Jensen et al. reported that the EBOV proteins VP40 and GP1/2 activate endothelial cells and impair barrier integrity, an effect exacerbated by tumor necrosis factor alpha (TNF-α), which reduces barrier function by approximately 30%. Conversely, sGP treatment following TNF-α exposure partially restores endothelial barrier function by about 20% [84]. Thus, sGP appears to exert an anti-inflammatory effect by preserving endothelial integrity and promoting barrier repair, potentially facilitating viral replication.

Another study demonstrated that sGP suppresses the production of pro-inflammatory cytokines in macrophages without altering the secretion of anti-inflammatory cytokines [87]. Moreover, while sGP does not impact phagocytic capacity, it significantly inhibits macrophage chemotaxis upon activation [87]. Collectively, these findings suggest that sGP suppresses effector cell activity prior to immune cell infection, thereby expanding the pool of susceptible target cells conducive to viral dissemination. The preservation of macrophage phagocytic function supports continued internalization of viral particles, thereby facilitating subsequent infection.

In summary, the anti-inflammatory properties of sGP are thought to establish a more immune-privileged niche within infected cells, promoting EBOV replication and favoring cell-to-cell viral dissemination.

4.4. sGP Facilitates EBOV Infection and Replication

One study demonstrated that in HEK293 kidney cells, sGP may enhance viral internalization by interacting with an unidentified cell surface molecule, significantly increasing the efficiency of EBOV particle entry into Rab7-positive late endosomes [80]. In Huh7 liver cells, sGP triggers phosphorylation of MEK1/2 (Dual specificity mitogen-activated protein kinase kinase 1/2) at Ser217/221, activating the MAPK (Mitogen-Activated Protein Kinase) pathway and leading to a 2- to 3-fold increase in both the number and size of EBOV infection foci. This enhancing effect was completely abolished by the MEK1/2 inhibitor Trametinib. Using a recombinant EBOV-sGP-KO-GFP virus, it was observed that addition of EBOV sGP dose-dependently increased the infectivity of EBOV-GFP in both HEK293 and Huh7 cells, accompanied by a significant enlargement of viral plaques. Notably, the enhancing effect of EBOV sGP was observed in both cell lines, with a more pronounced impact in Huh7 cells.

The sGP-mediated activation of the MAPK pathway may have profound implications for host metabolic dysregulation. MAPK signaling is a master regulator of cellular metabolism, controlling glucose uptake via GLUT4 (Glucose Transporter Type 4) translocation, insulin sensitivity through IRS-1 (Insulin Receptor Substrate 1) modulation, and lipid metabolism via PPARγ (Peroxisome Proliferator-Activated Receptor γ) and SREBP-1c (Sterol Regulatory Element-Binding Protein 1c) transcriptional activity [81,88,89]. Therefore, sustained MAPK activation induced by sGP could contribute to the severe metabolic disturbances observed in Ebola virus disease, including virus-induced hypoglycemia resulting from dysregulated glucose homeostasis, and lipid abnormalities such as the depletion of beneficial lipoproteins observed in fatal EVD cases [90]. The more pronounced effect observed in Huh7 liver cells aligns with the liver's central role in metabolic regulation, suggesting that sGP may specifically target hepatic metabolic pathways to create a more favorable environment for viral replication.

In animal models, administration of sGP following EBOV infection resulted in markedly elevated viral titers—approximately 100-fold higher in the liver (an effect comparable to that of the MAPK activator PMA

(Phorbol 12-myristate 13-acetate) and roughly 5-fold greater in the spleen—compared to untreated controls [80]. The striking similarity between sGP and PMA effects in the liver suggests that sGP-driven MAPK activation recapitulates the metabolic reprogramming induced by this potent phorbol ester, potentially diverting hepatic resources from metabolic homeostasis toward pathways that support viral replication [91]. This metabolic hijacking may explain the profound hepatocyte dysfunction and metabolic liver disease observed in severe EVD. In contrast, studies using sGP-deficient recombinant EBOV have yielded conflicting results. One study demonstrated that recombinant EBOV lacking sGP exhibited increased synthesis of GP1/2 at the cellular level, which led to enhanced cytotoxicity associated with elevated GP1/2 expression. However, guinea pigs infected with this sGP-deficient recombinant virus displayed lower viral loads throughout the experimental period compared to those infected with wild-type virus [92]. This finding suggests that sGP may play an important role in EBOV infection, or alternatively, that the cytotoxic effects of GP1/2 impose constraints on EBOV infection and dissemination. Conversely, another study found no significant attenuation of sGP-deficient recombinant EBOV in guinea pigs, reporting that the infectivity of the recombinant virus lacking sGP was unaffected [93]. The reason for the discrepancy between these two studies remains unclear, but it may be attributed to differences in the recombinant viruses used, variations in the guinea pig strains, or limitations inherent to the animal model employed.

Collectively, the role of sGP during EBOV infection remains to be fully elucidated, and current findings in the field are inconclusive. The precise mechanisms by which sGP contributes to viral entry, infection, replication, and modulation of the host microenvironment are not yet definitively established. Nevertheless, the presence of sGP at high concentrations (~100 μg/mL) in infected hosts underscores its potential biological significance. The convergence of sGP-mediated MAPK activation with the well-established metabolic complications of EVD suggests that sGP may function as a viral metabolic reprogramming factor, orchestrating host cellular metabolism to favor viral propagation while contributing to the systemic metabolic collapse characteristic of fatal infections. Therefore, further mechanistic studies are needed to clarify the specific functions and unique contributions of sGP to EBOV pathogenesis, which may guide development of interventions against sGP. Accordingly, we propose a unified hypothesis in this work to explain these seemingly contradictory results and functions of sGP.

4.5. A Dynamic Model of sGP Function and Therapeutic Potential

These controversial experimental outcomes mentioned above suggest that a new hypothesis may be required to provide a unified and coherent explanation for the function of sGP. Here, we base on existing studies regarding sGP's functions, which suggest its role may be stage-dependent, we propose a unifying "temporal regulation model". In this model, sGP exerts anti-inflammatory effects and promotes endothelial barrier repair during the early stages of infection, thereby creating a favorable microenvironment for viral propagation. Conversely, during the late viremic phase, sGP acts as a high-titer antibody sink, sequestering antibodies and effectively neutralizing their activity against viral particles. It is precisely this antibody incapacitation in the late stage that contributes to rapid disease progression; following the viral burst, severe symptoms emerge swiftly, often leading to rapid patient deterioration and death.

In light of the potential roles of sGP in facilitating viral infection or exacerbating disease, therapeutic strategies should be developed to target it directly. One promising approach is the development of antibodies directed against the unique C-terminal region of sGP. Such antibodies could be efficiently discovered using phage display technology to ensure high specificity. A key advantage of this strategy is that these anti-sGP antibodies would not compete with antibodies targeting the viral particle GP. By specifically clearing or neutralizing sGP, this treatment aims to liberate antibodies sequestered by the sGP "sink", thereby enhancing the effective neutralizing capacity against the virus itself. Alternatively, directly eliminating sGP could alleviate its putative immunosuppressive effects.

5. Roles of ADCC and ADCP in Protection against Ebola Virus Disease

Data from EVD models in infected humans and non-human primates (NHPs) indicate that survivors mount effective humoral and cell-mediated immune responses against EBOV antigens [94,95]. Among these responses, antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) represent critical cell-mediated immune mechanisms in anti-EBOV immunity [96].

One study demonstrated a strong positive correlation between the capacity of anti-EBOV GP monoclonal antibodies to clear EBOV-infected cells and their *in vitro* ADCC activity [97]. In a comprehensive global analysis conducted through the Viral Hemorrhagic Fever Immunotherapy Consortium, Erica et al. evaluated 171 anti-EBOV monoclonal antibodies and revealed an inverse correlation between the strength of Fc-mediated effector functions and the proximity of the antibody epitope to the viral membrane. Specifically, antibodies targeting the

glycan cap epitope exhibited the strongest ADCP activity, while those recognizing the head domain demonstrated superior NK cell activation [38]. Moreover, the multifunctional antibody responses—including ADCP and NK cell activation—were significantly positively correlated with protective efficacy in mouse models [38].

A separate study focusing on survivors of Bundibugyo virus (BDBV) infection revealed a significant inverse correlation between an elevated inflammatory state and reduced antibody-dependent cellular phagocytosis (ADCP), suggesting that excessive inflammation may suppress antibody-mediated effector functions [96].

Collectively, these findings underscore the critical role of antibody Fc effector functions, such as ADCC and ADCP, in mediating *in vivo* protection against EBOV. This understanding provides a clearer framework and more rational criteria for the selection and development of therapeutic antibodies with enhanced efficacy against EBOV infection.

6. Nanobodies Targeting the EBOV Glycoprotein (GP)

Nanobodies (Nbs), derived from the variable domains of heavy-chain-only antibodies (VHH) naturally found in camelids (e.g., llamas, camels) and sharks, have recently emerged as a novel class of antibodies with significant potential in virology, particularly in EBOV research. Compared to conventional IgG antibodies (~150 kDa), nanobodies are notably smaller (12–15 kDa) and exhibit several advantageous properties including superior access to sterically restricted or cryptic epitopes, high structural stability, enhanced tissue penetration capability, and ease of genetic engineering [98]. Their small size and robust stability not only facilitate deep tissue penetration but also make them amenable to alternative delivery routes, such as nebulization for pulmonary administration—a promising strategy for rapid post-exposure prophylaxis or treatment in resource-limited settings. These attributes make them especially attractive as candidates for therapeutic and diagnostic applications against highly pathogenic viruses such as EBOV.

Wang et al. identified a novel nanobody named M24, which exhibited potent neutralizing activity against recombinant VSV expressing EBOV GP, with an $IC50$ of 0.8 nM [99]. More recently, Bu et al. described two nanobodies, Nanosota-EB1 and Nanosota-EB2. EB1 is proposed to inhibit EBOV entry by stabilizing the glycan cap, potentially preventing its cleavage by cathepsins, whereas EB2 binding increases the energy barrier for the conformational transition of GPCL from the prefusion to postfusion state, thereby blocking EBOV cellular entry [100]. In a subsequent study, Wang et al. reported the identification of two additional nanobodies, 1A10 and BA2, through camel immunization and phage display [101]. Both antibodies demonstrated broad-spectrum neutralization against EBOV, SUDV, and BDBV, with $IC50$ values ranging from 1.5 to 30 nM against pseudoviruses and 1.9 to 31.3 nM against authentic viruses. Cryo-EM structures revealed that 1A10 binds near the GP1 base and the internal fusion loop (IFL), partially overlapping with the epitope of rEBOV-515, while BA2 targets the highly conserved fusion peptide of GP2, spanning two adjacent protomers. Mechanistically, 1A10 was shown to interfere with multiple steps of viral entry—including GP cleavage and NPC1 binding—whereas BA2 primarily inhibited attachment and membrane fusion. Building on these findings, the authors engineered a bispecific nanobody (BA2-1A10-Fc) by linking the two nanobodies via a GS linker and fusing to an IgG1 Fc domain. This bispecific construct exhibited markedly enhanced neutralization potency, particularly against SUDV (38-fold improvement over 1A10 alone), and conferred up to 100% protection in rodent models against EBOV, SUDV, and VSV-BDBV, even under delayed treatment conditions. Importantly, viral escape studies showed that the bispecific antibody suppressed the emergence of escape mutations, underscoring its potential as a broadly protective therapeutic against divergent ebolaviruses.

Nanobodies are emerging as a prominent modality in therapeutic antibody research. As this field advances, EBOV nanobody studies are progressively advancing from initial discovery phases toward structure-based rational design, cocktail formulations, broad-spectrum cross-species neutralization, and intelligent protein engineering. Future developments leveraging cross-reactive epitope targeting, multivalent architectures, and synergistic cocktail regimens hold considerable potential to address existing limitations of monoclonal antibody therapies. Such innovations could enable the development of low-cost, broadly effective, and accessible treatment and prophylactic options for Ebola virus disease.

7. Discussion

In this study, we systematically evaluated the current progress and limitations in the therapeutic landscape for EVD. Although monoclonal antibody therapies, such as REGN-EB3 and mAb114, have demonstrated significant survival benefits in randomized controlled trials, reducing mortality to approximately 35%, current treatment regimens still face multiple challenges [56]. Firstly, a distinct efficacy ceiling exists, as the effectiveness of these therapies remains limited for late-stage patients, particularly those presenting with high viral load and markers of organ impairment, such as elevated serum creatinine levels. Secondly, persistent viral evolution poses a substantial threat, with studies reporting the emergence of viral escape mutations under the selective pressure of

mAb therapy, potentially diminishing the efficacy of GP-targeting antibodies. Thirdly, a critical accessibility hurdle persists; all current effective mAb-based regimens require intravenous infusion and stringent cold-chain storage, creating profound logistical obstacles for deployment in resource-limited outbreak settings with weak infrastructure. These challenges were starkly illustrated in the most recent EVD outbreak in the Democratic Republic of the Congo, which began in September 2025 in Bulape Health Zone, Kasai Province—the country's 16th EVD outbreak. This new zoonotic spillover event of Zaire ebolavirus resulted in 64 cases (53 confirmed and 11 probable) and 45 deaths (case fatality rate: 70.3%), with infection and fatalities reported among healthcare workers and children under 10 years disproportionately affected [8]. Despite the availability of approved monoclonal antibody therapies, the outbreak—declared over in December 2025—demonstrated that even with coordinated international response efforts, the virus continues to exact a heavy toll, reinforcing the urgent need for next-generation countermeasures. Future research should therefore focus on developing combination therapies to enhance efficacy and mitigate resistance risks, optimizing drug formulations to improve suitability for resource-constrained environments, and exploring broadly neutralizing antibodies targeting conserved viral epitopes to counter the continuously evolving viral threat.

The EBOV GP is an extensively glycosylated protein with dozens of glycosylation sites, some of which carry over 40 distinct glycan compositions. Glycosylation critically influences GP functional activity, mediates epitope masking, and impedes antibody binding. The inherent heterogeneity and dynamic nature of glycosylation result in GP adopting multiple conformations. Certain neutralizing epitopes become accessible only under specific conditions—such as within the low-pH environment of endosomes following endocytosis—posing substantial challenges for the development of effective neutralizing antibodies. Consequently, the design of neutralizing antibodies against EBOV GP must account for the modulatory role of glycans in antibody–GP interactions and incorporate strategies to circumvent these obstacles. For example, developing "glycan-penetrating" antibodies that optimize complementary shape fitting, introduce glycan-binding residues, and utilize unique rigid β-hairpin structures to penetrate the dense glycan barrier of HIV Env proteins [102]. Such designs target cryptic glycan–peptide epitopes and may enable more potent viral neutralization.

Antibodies targeting different epitopes on the GP employ diverse mechanisms to neutralize the virus, but their broad-spectrum activity often depends on the evolutionary conservation of their target binding sites across Ebolavirus species. Therefore, prioritizing antibodies that engage conserved sequences is essential for developing broad-spectrum therapeutics against Ebola virus disease. Conventional views suggested that epitopes within relatively variable regions—such as the head domain and base domain—typically do not elicit broadly neutralizing antibodies. However, emerging evidence indicates that even these domains contain isolated conserved residues, and antibodies targeting these sites, such as 1C3 (head domain) and rEBOV-515 (base domain), can exhibit cross-reactive neutralization. In contrast, the fusion loop and HR2/MPER domains, which exhibit high sequence conservation across species, represent promising targets for the development of broadly neutralizing antibodies against EBOV.

The majority of potent broad-spectrum neutralizing antibodies currently identified against EBOV—including rEBOV-520/548, rEBOV-442/515, BDBV289, CA45, ADI15878/15946, and 1C3/1C11—were isolated from convalescent sera of survivors of the 2014–2016 Ebola outbreak. In the development of EBOV-targeting antibodies, the strategy of isolating antibodies from memory B cells of human survivors has consistently demonstrated superior efficacy compared to alternative approaches, such as harvesting B cells from immunized mice or screening synthetic phage display libraries. Nonetheless, the limited availability of convalescent samples from the 2014–2016 outbreak poses a substantial constraint on the advancement of such studies on a global scale.

A significant advance in addressing the aforementioned resource limitations is the application of artificial intelligence (AI) to design highly potent broad-spectrum neutralizing antibodies against EBOV. Using convolutional neural networks, graph neural networks, and generative AI models, it is possible to predict potential neutralizing epitopes on the GP, enabling rapid *in silico* screening and *de novo* antibody sequence design. Coupled with structural modeling tools like AlphaFold3 to resolve the GP-antibody complex structure, the complementarity between the antibody paratope and the epitope can be systematically optimized. Molecular dynamics simulations can further assess the stability of antibody–GP binding and evaluate the impact of glycan shielding on these interactions. This integrated computational approach holds promise for designing antibody-based therapeutics that meet clinical needs and reduce mortality among infected patients. Nevertheless, despite these advances, experimental validation and optimization through wet-lab studies remain essential to confirm the efficacy and specificity of AI-designed antibodies. Furthermore, leveraging the computational power of AI, deep generative models trained on historical viral sequences—incorporating structural and biophysical constraints—can provide continuously updated escape scores for all EBOV subtypes. Such models are capable of predicting prospective mutations, including those in emerging strains, thereby supporting proactive vaccine and therapeutic development [103]. For instance, deep learning

architectures such as variational autoencoders (VAEs) and graph neural networks (GNNs) are capable of integrating the vast datasets generated by deep mutational scanning experiments. By analyzing the dual impact of mutations on viral fitness and antibody binding, AI can construct complex "Maps of Coordinated Escape". This approach not only identifies escape hotspots for individual antibodies but also predicts the most probable "evolutionary shortcuts"—such as single mutations that confer simultaneous resistance to multiple antibodies—that the virus might take under the selective pressure of combination therapies (e.g., antibody cocktails). Consequently, it provides crucial insights for designing antibody combinations with a high genetic barrier to resistance. This strategy may offer early warnings concerning immune evasion mutations and facilitate the design of more effective countermeasures against future outbreaks.

Cocktail antibodies offer substantial advantages in counteracting viral escape. The high mutation rates characteristic of RNA viruses frequently lead to escape mutations at singular therapeutic targets, whereas multi-epitope targeting significantly raises the genetic barrier to resistance by requiring concurrent mutations at multiple sites. Furthermore, by engaging conserved epitopes on viral proteins, antibody cocktails enhance neutralization breadth across diverse viral strains. Additionally, the combination of different drugs or antibodies may produce a synergistic effect, which can operate through spatial and functional cooperation. Additional benefits may include synergistic mechanisms arising from spatial and functional cooperativity—for instance, the binding of one antibody may induce conformational changes in GP, thereby unmasking cryptic epitopes and enhancing neutralization by other components. Meanwhile, Fc-mediated effector functions (such as ADCC, ADCP) contribute to the clearance of infected cells, thereby leveraging the full functional potential of each antibody within the cocktail. Several therapeutic antibody combinations, including Zmapp [39], REGN-EB3 [42], FVM04/CA45 [104], MBP134 [105], MB-003 [106], rEBOV-520/548 [107], rEBOV-442/515 [44], and 1C3/1C11 [45], have been developed and demonstrate robust protection in non-human primate challenge models.

mRNA delivery technology marks a paradigm shift in Ebola virus disease prophylaxis by transitioning from passive antibody infusion to *in situ* production, thereby overcoming the pharmacokinetic limitations of traditional biologics such as short half-life and poor biodistribution. Preclinical data from Fan et al. demonstrate that an LNP-encapsulated mRNA encoding the broad-spectrum antibody 2G1 achieves rapid *in vivo* expression and exhibits 19.8-fold and 12.5-fold higher neutralization potency against Ebola and Sudan virus pseudotypes, respectively, compared to its recombinant IgG counterpart. This enhanced efficacy likely stems from sustained antibody production *in situ*, human-cell-specific glycosylation optimizing Fc effector functions, and more effective viral interception during cell-to-cell spread. From a public health standpoint, the platform's agility enables rapid, sequence-based design within weeks, offering critical advantages for outbreak response and post-exposure prophylaxis, while ongoing LNP innovations promise to overcome cold-chain barriers and enable scalable manufacturing—transforming biologics from stockpiled commodities into on-demand countermeasures. However, the intrinsic adjuvanticity of mRNA-LNP complexes poses immunogenicity risks that may shorten expression duration or induce inflammatory toxicities. Thus, future development must balance high translation efficiency with minimized innate immune sensing through refined backbone design and LNP formulation to fully realize this platform's potential for equitable, durable Ebola countermeasures.

8. Conclusions and Prospective

In real-world settings, EBOV infection is characterized by an incubation period during which clinical manifestations are highly similar to those of influenza, complicating early diagnosis. Identification of infection currently relies primarily on travel history to endemic regions followed by laboratory confirmation via RT-PCR (Reverse Transcription-Polymerase Chain Reaction) assays. There are no widely available, non-laboratory methods for the public to independently determine infection status. Consequently, by the time Ebola virus disease is diagnosed, patients often present with acute symptoms and may have already contributed to community transmission, significantly impeding outbreak containment efforts. This diagnostic delay is a key factor contributing to the persistently high case fatality rate of approximately 35%, even with advanced clinical interventions. Under experimental conditions, antibody therapies are typically administered no later than two days post-infection in non-human primate models, a scenario that does not adequately recapture the typical clinical timeline of human cases. Thus, many antibodies demonstrating high efficacy in laboratory settings may show reduced effectiveness in real-world applications. It is therefore critical to develop novel antibody therapeutics that better align with clinical realities, establish more physiologically and temporally relevant animal models and treatment windows, and create point-of-care tools capable of detecting EBOV infection during the early incubation phase. These challenges are garnering increasing attention and are expected to remain central research priorities in the field.

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References

1. Dhama, K.; Malik, Y.S.; Malik, S.V.S.; Singh, R.K. Ebola from emergence to epidemic: The virus and the disease, global preparedness and perspectives. *J. Infect. Dev. Ctries.* **2015**, *9*, 441–455. https://doi.org/10.3855/jidc.6197.
2. Jacob, S.T.; Crozier, I.; Fischer, W.A.; Hewlett, A.; Kraft, C.S.; Vega, M.-A.D.L.; Soka, M.J.; Wahl, V.; Griffiths, A.; Bollinger, L.; et al. Ebola virus disease. *Nat. Rev. Dis. Primers* **2020**, *6*, 13. https://doi.org/10.1038/s41572-020-0147-3.
3. Kofman, A.; Linderman, S.; Su, K.; Purpura, L.J.; Ervin, E.; Brown, S.; Morales-Betoulle, M.; Graziano, J.; Cannon, D.L.; Klena, J.D.; et al. Characteristics of Ebola Virus Disease Survivor Blood and Semen in Liberia: Serology and Reverse Transcription Polymerase Chain Reaction (RT-PCR). *Clin. Infect. Dis.* **2021**, *73*, e3641–e3646. https://doi.org/10.1093/cid/ciaa1331.
4. Letafati, A.; Salahi Ardekani, O.; Karami, H.; Soleimani, M. Ebola virus disease: A narrative review. *Microb. Pathog.* **2023**, *181*, 106213. https://doi.org/10.1016/j.micpath.2023.106213.
5. Kiley, M.P.; Bowen, E.T.W.; Eddy, G.A.; Isaäcson, M.; Johnson, K.M.; McCormick, J.B.; Murphy, F.A.; Pattyn, S.R.; Peters, D.; Prozesky, O.W.; et al. Filoviridae: A Taxonomic Home for Marburg and Ebola Viruses? *Intervirology* **1982**, *18*, 24–32. https://doi.org/10.1159/000149300.
6. Camacho, A.; Kucharski, A.J.; Funk, S.; Breman, J.; Piot, P.; Edmunds, W.J. Potential for large outbreaks of Ebola virus disease. *Epidemics* **2014**, *9*, 70–78. https://doi.org/10.1016/j.epidem.2014.09.003.
7. Cross, R.W.; Woolsey, C.; Chu, V.C.; Babusis, D.; Bannister, R.; Vermillion, M.S.; Geleziunas, R.; Barrett, K.T.; Bunyan, E.; Nguyen, A.-Q.; et al. Oral administration of obeldesivir protects nonhuman primates against Sudan ebolavirus. *Science* **2024**, *383*, eadk6176. https://doi.org/10.1126/science.adk6176.
8. Mwamba, D.K.; Angendu, K.B.; Diouf, W.; Mikobi, M.-C.; Leonard, O.; Kalala, D.; Ntumba, N.; Kakule, D.; Kayembe, D.K.; Sana, E.; et al. Seven Strategies Implemented in Response to the 16th Ebola Virus Disease Outbreak in the Democratic Republic of Congo: Lessons Learned over a Three-Month Period. *Viruses* **2025**, *18*, 28. https://doi.org/10.3390/v18010028.
9. Beeching, N.J.; Fenech, M.; Houlihan, C.F. Ebola virus disease. *BMJ* **2014**, *349*, g7348. https://doi.org/10.1136/bmj.g7348.
10. Campion, E.W.; Feldmann, H.; Sprecher, A.; Geisbert, T.W. Ebola. *N. Engl. J. Med.* **2020**, *382*, 1832–1842. https://doi.org/10.1056/NEJMra1901594.
11. Muwonge, H.; Nasimiyu, C.; Bakamutumaho, B.; Elyanu, P.; Joloba, M.L.; Situma, S.; Schieffelin, J.; Gunn, B.; Bai, S.; Breiman, R.F.; et al. Severe long-term clinical sequelae among Sudan ebolavirus disease survivors 2 years post-infection. *BMC* Med. **2025**, *23*, 432.
12. Lee, J.E.; Saphire, E.O. Ebolavirus Glycoprotein Structure and Mechanism of Entry. *Future Virol.* **2009**, *4*, 621–635. https://doi.org/10.2217/fvl.09.56.
13. Takada, A.; Watanabe, S.; Ito, H.; Okazaki, K.; Kida, H.; Kawaoka, Y. Downregulation of β1 Integrins by Ebola Virus Glycoprotein: Implication for Virus Entry. *Virology* **2000**, *278*, 20–26. https://doi.org/10.1006/viro.2000.0601.
14. Alvarez, C.P.; Lasala, F.; Carrillo, J.; Muñiz, O.; Corbí, A.L.; Delgado, R. C-Type Lectins DC-SIGN and L-SIGN Mediate Cellular Entry by Ebola Virus in cis and in trans. *J. Virol.* **2002**, *76*, 6841–6844. https://doi.org/10.1128/JVI.76.13.6841-6844.2002.
15. Usami, K.; Matsuno, K.; Igarashi, M.; Denda-Nagai, K.; Takada, A.; Irimura, T. Involvement of viral envelope GP2 in Ebola virus entry into cells expressing the macrophage galactose-type C-type lectin. *Biochem. Biophys. Res. Commun.* **2011**, *407*, 74–78. https://doi.org/10.1016/j.bbrc.2011.02.110.

16. Kondratowicz, A.S.; Lennemann, N.J.; Sinn, P.L.; Davey, R.A.; Hunt, C.L.; Moller-Tank, S.; Meyerholz, D.K.; Rennert, P.; Mullins, R.F.; Brindley, M.; et al. T-cell immunoglobulin and mucin domain 1 (TIM-1) is a receptor for Zaire Ebolavirus and Lake Victoria Marburgvirus. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 8426–8431. https://doi.org/10.1073/pnas.1019030108.
17. Brudner, M.; Karpel, M.; Lear, C.; Chen, L.; Yantosca, L.M.; Scully, C.; Sarraju, A.; Sokolovska, A.; Zariffard, M.R.; Eisen, D.P.; et al. Lectin-Dependent Enhancement of Ebola Virus Infection via Soluble and Transmembrane C-type Lectin Receptors. *PLoS ONE* **2013**, *8*, e60838. https://doi.org/10.1371/journal.pone.0060838.
18. Simmons, G.; Reeves, J.D.; Grogan, C.C.; Vandenberghe, L.H.; Baribaud, F.; Whitbeck, J.C.; Burke, E.; Buchmeier, M.J.; Soilleux, E.J.; Riley, J.L.; et al. DC-SIGN and DC-SIGNR Bind Ebola Glycoproteins and Enhance Infection of Macrophages and Endothelial Cells. *Virology* **2003**, *305*, 115–123. https://doi.org/10.1006/viro.2002.1730.
19. Takada, A.; Fujioka, K.; Tsuiji, M.; Morikawa, A.; Higashi, N.; Ebihara, H.; Kobasa, D.; Feldmann, H.; Irimura, T.; Kawaoka, Y. Human Macrophage C-Type Lectin Specific for Galactose and N-Acetylgalactosamine Promotes Filovirus Entry. *J. Virol.* **2004**, *78*, 2943–2947. https://doi.org/10.1128/JVI.78.6.2943-2947.2004.
20. Lee, J.E.; Fusco, M.L.; Hessell, A.J.; Oswald, W.B.; Burton, D.R.; Saphire, E.O. Structure of the Ebola virus glycoprotein bound to an antibody from a human survivor. *Nature* **2008**, *454*, 177–182. https://doi.org/10.1038/nature07082.
21. Dube, D.; Brecher, M.B.; Delos, S.E.; Rose, S.C.; Park, E.W.; Schornberg, K.L.; Kuhn, J.H.; White, J.M. The Primed Ebolavirus Glycoprotein (19-Kilodalton GP1,2): Sequence and Residues Critical for Host Cell Binding. *J. Virol.* **2009**, *83*, 2883–2891. https://doi.org/10.1128/JVI.01956-08.
22. Schornberg, K.L.; Shoemaker, C.J.; Dube, D.; Abshire, M.Y.; Delos, S.E.; Bouton, A.H.; White, J.M. α5 β1-Integrin controls ebolavirus entry by regulating endosomal cathepsins. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 8003–8008. https://doi.org/10.1073/pnas.0807578106.
23. Brindley, M.A.; Hunt, C.L.; Kondratowicz, A.S.; Bowman, J.; Sinn, P.L.; McCray, P.B.; Quinn, K.; Weller, M.L.; Chiorini, J.A.; Maury, W. Tyrosine kinase receptor Axl enhances entry of Zaire ebolavirus without direct interactions with the viral glycoprotein. *Virology* **2011**, *415*, 83–94. https://doi.org/10.1016/j.virol.2011.04.002.
24. Hunt, C.L.; Kolokoltsov, A.A.; Davey, R.A.; Maury, W. The Tyro3 Receptor Kinase Axl Enhances Macropinocytosis of Zaire Ebolavirus. *J. Virol.* **2011**, *85*, 334–347. https://doi.org/10.1128/JVI.01278-09.
25. Nanbo, A.; Imai, M.; Watanabe, S.; Noda, T.; Takahashi, K.; Neumann, G.; Halfmann, P.; Kawaoka, Y. Ebolavirus Is Internalized into Host Cells via Macropinocytosis in a Viral Glycoprotein-Dependent Manner. *PLoS Pathog.* **2010**, *6*, e1001121. https://doi.org/10.1371/journal.ppat.1001121.
26. Aleksandrowicz, P.; Marzi, A.; Biedenkopf, N.; Beimforde, N.; Becker, S.; Hoenen, T.; Feldmann, H.; Schnittler, H.-J. Ebola Virus Enters Host Cells by Macropinocytosis and Clathrin-Mediated Endocytosis. *J. Infect. Dis.* **2011**, *204*, S957–S967. https://doi.org/10.1093/infdis/jir326.
27. Zhang, Q.; Tian, F.; Wang, F.; Guo, Z.; Cai, M.; Xu, H.; Wang, H.; Yang, G.; Shi, X.; Shan, Y.; et al. Entry Dynamics of Single Ebola Virus Revealed by Force Tracing. *ACS Nano* **2020**, *14*, 7046–7054. https://doi.org/10.1021/acsnano.0c01739.
28. Sanchez, A. Analysis of Filovirus Entry into Vero E6 Cells, Using Inhibitors of Endocytosis, Endosomal Acidification, Structural Integrity, and Cathepsin (B and L) Activity. *J. Infect. Dis.* **2007**, *196*, S251–S258. https://doi.org/10.1086/520597.
29. Kaletsky, R.L.; Simmons, G.; Bates, P. Proteolysis of the Ebola Virus Glycoproteins Enhances Virus Binding and Infectivity. *J. Virol.* **2007**, *81*, 13378–13384. https://doi.org/10.1128/JVI.01170-07.
30. Schornberg, K.; Matsuyama, S.; Kabsch, K.; Delos, S.; Bouton, A.; White, J. Role of Endosomal Cathepsins in Entry Mediated by the Ebola Virus Glycoprotein. *J. Virol.* **2006**, *80*, 4174–4178. https://doi.org/10.1128/JVI.80.8.4174-4178.2006.
31. Chandran, K.; Sullivan, N.J.; Felbor, U.; Whelan, S.P.; Cunningham, J.M. Endosomal Proteolysis of the Ebola Virus Glycoprotein Is Necessary for Infection. *Science* **2005**, *308*, 1643–1645. https://doi.org/10.1126/science.1110656.
32. Saeed, M.F.; Kolokoltsov, A.A.; Albrecht, T.; Davey, R.A. Cellular Entry of Ebola Virus Involves Uptake by a Macropinocytosis-Like Mechanism and Subsequent Trafficking through Early and Late Endosomes. *PLoS Pathog.* **2010**, *6*, e1001110. https://doi.org/10.1371/journal.ppat.1001110.
33. Carette, J.E.; Raaben, M.; Wong, A.C.; Herbert, A.S.; Obernosterer, G.; Mulherkar, N.; Kuehne, A.I.; Kranzusch, P.J.; Griffin, A.M.; Ruthel, G.; et al. Ebola virus entry requires the cholesterol transporter Niemann–Pick C1. *Nature* **2011**, *477*, 340–343. https://doi.org/10.1038/nature10348.
34. Côté, M.; Misasi, J.; Ren, T.; Bruchez, A.; Lee, K.; Filone, C.M.; Hensley, L.; Li, Q.; Ory, D.; Chandran, K.; et al. Small molecule inhibitors reveal Niemann–Pick C1 is essential for Ebola virus infection. *Nature* **2011**, *477*, 344–348. https://doi.org/10.1038/nature10380.

35. Miller, E.H.; Obernosterer, G.; Raaben, M.; Herbert, A.S.; Deffieu, M.S.; Krishnan, A.; Ndungo, E.; Sandesara, R.G.; Carette, J.E.; Kuehne, A.I.; et al. Ebola virus entry requires the host-programmed recognition of an intracellular receptor: Niemann-Pick C1 is a critical filovirus receptor. *EMBO J.* **2012**, *31*, 1947–1960. https://doi.org/10.1038/emboj.2012.53.
36. Wang, H.; Shi, Y.; Song, J.; Qi, J.; Lu, G.; Yan, J.; Gao, G.F. Ebola Viral Glycoprotein Bound to Its Endosomal Receptor Niemann-Pick C1. *Cell* **2016**, *164*, 258–268. https://doi.org/10.1016/j.cell.2015.12.044.
37. Jun, S.-R.; Leuze, M.R.; Nookaew, I.; Uberbacher, E.C.; Land, M.; Zhang, Q.; Wanchai, V.; Chai, J.; Nielsen, M.; Trolle, T.; et al. Ebolavirus comparative genomics. *FEMS Microbiol. Rev.* **2015**, *39*, 764–778. https://doi.org/10.1093/femsre/fuv031.
38. Saphire, E.O.; Schendel, S.L.; Fusco, M.L.; Gangavarapu, K.; Gunn, B.M.; Wec, A.Z.; Halfmann, P.J.; Brannan, J.M.; Herbert, A.S.; Qiu, X.; et al. Systematic Analysis of Monoclonal Antibodies against Ebola Virus GP Defines Features that Contribute to Protection. *Cell* **2018**, *174*, 938–952.e13. https://doi.org/10.1016/j.cell.2018.07.033.
39. Qiu, X.; Wong, G.; Audet, J.; Bello, A.; Fernando, L.; Alimonti, J.B.; Fausther-Bovendo, H.; Wei, H.; Aviles, J.; Hiatt, E.; et al. Reversion of advanced Ebola virus disease in nonhuman primates with ZMapp. *Nature* **2014**, *514*, 47–53. https://doi.org/10.1038/nature13777.
40. Corti, D.; Misasi, J.; Mulangu, S.; Stanley, D.A.; Kanekiyo, M.; Wollen, S.; Ploquin, A.; Doria-Rose, N.A.; Staupe, R.P.; Bailey, M.; et al. Protective monotherapy against lethal Ebola virus infection by a potently neutralizing antibody. *Science* **2016**, *351*, 1339–1342. https://doi.org/10.1126/science.aad5224.
41. Zhao, X.; Howell, K.A.; He, S.; Brannan, J.M.; Wec, A.Z.; Davidson, E.; Turner, H.L.; Chiang, C.-I.; Lei, L.; Fels, J.M.; et al. Immunization-Elicited Broadly Protective Antibody Reveals Ebolavirus Fusion Loop as a Site of Vulnerability. *Cell* **2017**, *169*, 891–904.e15. https://doi.org/10.1016/j.cell.2017.04.038.
42. Pascal, K.E.; Dudgeon, D.; Trefry, J.C.; Anantpadma, M.; Sakurai, Y.; Murin, C.D.; Turner, H.L.; Fairhurst, J.; Torres, M.; Rafique, A.; et al. Development of Clinical-Stage Human Monoclonal Antibodies That Treat Advanced Ebola Virus Disease in Nonhuman Primates. *J. Infect. Dis.* **2018**, *218*, S612–S626. https://doi.org/10.1093/infdis/jiy285.
43. Flyak, A.I.; Kuzmina, N.; Murin, C.D.; Bryan, C.; Davidson, E.; Gilchuk, P.; Gulka, C.P.; Ilinykh, P.A.; Shen, X.; Huang, K.; et al. Broadly neutralizing antibodies from human survivors target a conserved site in the Ebola virus glycoprotein HR2–MPER region. *Nat. Microbiol.* **2018**, *3*, 670–677. https://doi.org/10.1038/s41564-018-0157-z.
44. Gilchuk, P.; Murin, C.D.; Cross, R.W.; Ilinykh, P.A.; Huang, K.; Kuzmina, N.; Borisevich, V.; Agans, K.N.; Geisbert, J.B.; Zost, S.J.; et al. Pan-ebolavirus protective therapy by two multifunctional human antibodies. *Cell* **2021**, *184*, 5593–5607.e18. https://doi.org/10.1016/j.cell.2021.09.035.
45. Milligan, J.C.; Davis, C.W.; Yu, X.; Ilinykh, P.A.; Huang, K.; Halfmann, P.J.; Cross, R.W.; Borisevich, V.; Agans, K.N.; Geisbert, J.B.; et al. Asymmetric and non-stoichiometric glycoprotein recognition by two distinct antibodies results in broad protection against ebolaviruses. *Cell* **2022**, *185*, 995–1007.e18. https://doi.org/10.1016/j.cell.2022.02.023.
46. Zhang, Q.; Gui, M.; Niu, X.; He, S.; Wang, R.; Feng, Y.; Kroeker, A.; Zuo, Y.; Wang, H.; Wang, Y.; et al. Potent neutralizing monoclonal antibodies against Ebola virus infection. *Sci. Rep.* **2016**, *6*, 25856. https://doi.org/10.1038/srep25856.
47. Shedlock, D.J.; Bailey, M.A.; Popernack, P.M.; Cunningham, J.M.; Burton, D.R.; Sullivan, N.J. Antibody-mediated neutralization of Ebola virus can occur by two distinct mechanisms. *Virology* **2010**, *401*, 228–235. https://doi.org/10.1016/j.virol.2010.02.029.
48. Murin, C.D.; Fusco, M.L.; Bornholdt, Z.A.; Qiu, X.; Olinger, G.G.; Zeitlin, L.; Kobinger, G.P.; Ward, A.B.; Saphire, E.O. Structures of protective antibodies reveal sites of vulnerability on Ebola virus. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 17182–17187. https://doi.org/10.1073/pnas.1414164111.
49. Davidson, E.; Bryan, C.; Fong, R.H.; Barnes, T.; Pfaff, J.M.; Mabila, M.; Rucker, J.B.; Doranz, B.J. Mechanism of Binding to Ebola Virus Glycoprotein by the ZMapp, ZMAb, and MB-003 Cocktail Antibodies. *J. Virol.* **2015**, *89*, 10982–10992. https://doi.org/10.1128/JVI.01490-15.
50. West, B.R.; Wec, A.Z.; Moyer, C.L.; Fusco, M.L.; Ilinykh, P.A.; Huang, K.; Wirchnianski, A.S.; James, R.M.; Herbert, A.S.; Hui, S.; et al. Structural basis of broad ebolavirus neutralization by a human survivor antibody. *Nat. Struct. Mol. Biol.* **2019**, *26*, 204–212. https://doi.org/10.1038/s41594-019-0191-4.
51. Bornholdt, Z.A.; Ndungo, E.; Fusco, M.L.; Bale, S.; Flyak, A.I.; Crowe, J.E.; Chandran, K.; Saphire, E.O. Host-Primed Ebola Virus GP Exposes a Hydrophobic NPC1 Receptor-Binding Pocket, Revealing a Target for Broadly Neutralizing Antibodies. *mBio* **2016**, *7*, e02154-15. https://doi.org/10.1128/mBio.02154-15.
52. Audet, J.; Wong, G.; Wang, H.; Lu, G.; Gao, G.F.; Kobinger, G.; Qiu, X. Molecular Characterization of the Monoclonal Antibodies Composing ZMAb: A Protective Cocktail Against Ebola Virus. *Sci. Rep.* **2014**, *4*, 6881. https://doi.org/10.1038/srep06881.
53. Oswald, W.B.; Geisbert, T.W.; Davis, K.J.; Geisbert, J.B.; Sullivan, N.J.; Jahrling, P.B.; Parren, P.W.H.I.; Burton, D.R. Neutralizing Antibody Fails to Impact the Course of Ebola Virus Infection in Monkeys. *PLoS Pathog.* **2007**, *3*, e9. https://doi.org/10.1371/journal.ppat.0030009.

54. Misasi, J.; Gilman, M.S.A.; Kanekiyo, M.; Gui, M.; Cagigi, A.; Mulangu, S.; Corti, D.; Ledgerwood, J.E.; Lanzavecchia, A.; Cunningham, J.; et al. Structural and molecular basis for Ebola virus neutralization by protective human antibodies. *Science* **2016**, *351*, 1343–1346. https://doi.org/10.1126/science.aad6117.
55. Rayaprolu, V.; Fulton, B.O.; Rafique, A.; Arturo, E.; Williams, D.; Hariharan, C.; Callaway, H.; Parvate, A.; Schendel, S.L.; Parekh, D.; et al. Structure of the Inmazeb cocktail and resistance to Ebola virus escape. *Cell Host Microbe* **2023**, *31*, 260–272.e7. https://doi.org/10.1016/j.chom.2023.01.002.
56. Mulangu, S.; Dodd, L.E.; Davey, R.T.; Tshiani Mbaya, O.; Proschan, M.; Mukadi, D.; Lusakibanza Manzo, M.; Nzolo, D.; Tshomba Oloma, A.; Ibanda, A.; et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. *N. Engl. J. Med.* **2019**, *381*, 2293–2303. https://doi.org/10.1056/NEJMoa1910993.
57. Peng, W.; Rayaprolu, V.; Parvate, A.D.; Pronker, M.F.; Hui, S.; Parekh, D.; Shaffer, K.; Yu, X.; Saphire, E.O.; Snijder, J. Glycan shield of the ebolavirus envelope glycoprotein GP. *Commun. Biol.* **2022**, *5*, 785. https://doi.org/10.1038/s42003-022-03767-1.
58. Lin, G.; Simmons, G.; Pöhlmann, S.; Baribaud, F.; Ni, H.; Leslie, G.J.; Haggarty, B.S.; Bates, P.; Weissman, D.; Hoxie, J.A.; et al. Differential N-Linked Glycosylation of Human Immunodeficiency Virus and Ebola Virus Envelope Glycoproteins Modulates Interactions with DC-SIGN and DC-SIGNR. *J. Virol.* **2003**, *77*, 1337–1346. https://doi.org/10.1128/JVI.77.2.1337-1346.2003.
59. Collar, A.L.; Clarke, E.C.; Anaya, E.; Merrill, D.; Yarborough, S.; Anthony, S.M.; Kuhn, J.H.; Merle, C.; Theisen, M.; Bradfute, S.B. Comparison of N- and O-linked glycosylation patterns of ebolavirus glycoproteins. *Virology* **2017**, *502*, 39–47. https://doi.org/10.1016/j.virol.2016.12.010.
60. Dowling, W.; Thompson, E.; Badger, C.; Mellquist, J.L.; Garrison, A.R.; Smith, J.M.; Paragas, J.; Hogan, R.J.; Schmaljohn, C. Influences of Glycosylation on Antigenicity, Immunogenicity, and Protective Efficacy of Ebola Virus GP DNA Vaccines. *J. Virol.* **2007**, *81*, 1821–1837. https://doi.org/10.1128/JVI.02098-06.
61. Iraqi, M.; Edri, A.; Greenshpan, Y.; Kundu, K.; Bolel, P.; Cahana, A.; Ottolenghi, A.; Gazit, R.; Lobel, L.; Braiman, A.; et al. N-Glycans Mediate the Ebola Virus-GP1 Shielding of Ligands to Immune Receptors and Immune Evasion. *Front. Cell. Infect. Microbiol.* **2020**, *10*, 48. https://doi.org/10.3389/fcimb.2020.00048.
62. Jeffers, S.A.; Sanders, D.A.; Sanchez, A. Covalent Modifications of the Ebola Virus Glycoprotein. *J. Virol.* **2002**, *76*, 12463–12472. https://doi.org/10.1128/JVI.76.24.12463-12472.2002.
63. Lennemann, N.J.; Rhein, B.A.; Ndungo, E.; Chandran, K.; Qiu, X.; Maury, W. Comprehensive Functional Analysis of N-Linked Glycans on Ebola Virus GP1. *mBio* **2014**, *5*, e00862-13. https://doi.org/10.1128/mBio.00862-13.
64. Ritchie, G.; Harvey, D.J.; Stroeher, U.; Feldmann, F.; Feldmann, H.; Wahl-Jensen, V.; Royle, L.; Dwek, R.A.; Rudd, P.M. Identification of N-glycans from Ebola virus glycoproteins by matrix-assisted laser desorption/ionisation time-of-flight and negative ion electrospray tandem mass spectrometry. Rapid Commun. *Mass Spectrom.* **2010**, *24*, 571–585. https://doi.org/10.1002/rcm.4410.
65. Wang, B.; Wang, Y.; Frabutt, D.A.; Zhang, X.; Yao, X.; Hu, D.; Zhang, Z.; Liu, C.; Zheng, S.; Xiang, S.-H.; et al. Mechanistic understanding of N-glycosylation in Ebola virus glycoprotein maturation and function. *J. Biol. Chem.* **2017**, *292*, 5860–5870. https://doi.org/10.1074/jbc.M116.768168.
66. Gunn, B.M.; Yu, W.-H.; Karim, M.M.; Brannan, J.M.; Herbert, A.S.; Wec, A.Z.; Halfmann, P.J.; Fusco, M.L.; Schendel, S.L.; Gangavarapu, K.; et al. A Role for Fc Function in Therapeutic Monoclonal Antibody-Mediated Protection against Ebola Virus. *Cell Host Microbe* **2018**, *24*, 221–233.e5. https://doi.org/10.1016/j.chom.2018.07.009.
67. Ilinykh, P.A.; Huang, K.; Gunn, B.M.; Kuzmina, N.A.; Kedarinath, K.; Jurado-Cobena, E.; Zhou, F.; Subramani, C.; Hyde, M.A.; Velazquez, J.V.; et al. Antibodies targeting the glycan cap of Ebola virus glycoprotein are potent inducers of the complement system. *Commun. Biol.* **2024**, *7*, 871. https://doi.org/10.1038/s42003-024-06556-0.
68. Olal, D.; Kuehne, A.I.; Bale, S.; Halfmann, P.; Hashiguchi, T.; Fusco, M.L.; Lee, J.E.; King, L.B.; Kawaoka, Y.; Dye, J.M.; et al. Structure of an Antibody in Complex with Its Mucin Domain Linear Epitope That Is Protective against Ebola Virus. *J. Virol.* **2012**, *86*, 2809–2816. https://doi.org/10.1128/JVI.05549-11.
69. Gilchuk, P.; Murin, C.D.; Milligan, J.C.; Cross, R.W.; Mire, C.E.; Ilinykh, P.A.; Huang, K.; Kuzmina, N.; Altman, P.X.; Hui, S.; et al. Analysis of a Therapeutic Antibody Cocktail Reveals Determinants for Cooperative and Broad Ebolavirus Neutralization. *Immunity* **2020**, *52*, 388–403.e12. https://doi.org/10.1016/j.immuni.2020.01.001.
70. Wilson, J.A.; Hevey, M.; Bakken, R.; Guest, S.; Bray, M.; Schmaljohn, A.L.; Hart, M.K. Epitopes Involved in Antibody-Mediated Protection from Ebola Virus. *Science* **2000**, *287*, 1664–1666. https://doi.org/10.1126/science.287.5458.1664.
71. Wec, A.Z.; Bornholdt, Z.A.; He, S.; Herbert, A.S.; Goodwin, E.; Wirchnianski, A.S.; Gunn, B.M.; Zhang, Z.; Zhu, W.; Liu, G.; et al. Development of a Human Antibody Cocktail that Deploys Multiple Functions to Confer Pan-Ebolavirus Protection. *Cell Host Microbe* **2019**, *25*, 39–48.e5. https://doi.org/10.1016/j.chom.2018.12.004.
72. Lee, J.; Nyenhuis, D.A.; Nelson, E.A.; Cafiso, D.S.; White, J.M.; Tamm, L.K. Structure of the Ebola virus envelope protein MPER/TM domain and its interaction with the fusion loop explains their fusion activity. *Biophys. J.* **2017**, *112*, 78a. https://doi.org/10.1016/j.bpj.2016.11.468.

73. Wec, A.Z.; Herbert, A.S.; Murin, C.D.; Nyakatura, E.K.; Abelson, D.M.; Fels, J.M.; He, S.; James, R.M.; De La Vega, M.-A.; Zhu, W.; et al. Antibodies from a Human Survivor Define Sites of Vulnerability for Broad Protection against Ebolaviruses. *Cell* **2017**, *169*, 878–890.e15. https://doi.org/10.1016/j.cell.2017.04.037.
74. Flyak, A.I.; Shen, X.; Murin, C.D.; Turner, H.L.; David, J.A.; Fusco, M.L.; Lampley, R.; Kose, N.; Ilinykh, P.A.; Kuzmina, N.; et al. Cross-Reactive and Potent Neutralizing Antibody Responses in Human Survivors of Natural Ebolavirus Infection. *Cell* **2016**, *164*, 392–405. https://doi.org/10.1016/j.cell.2015.12.022.
75. Gilchuk, P.; Mire, C.E.; Geisbert, J.B.; Agans, K.N.; Deer, D.J.; Cross, R.W.; Slaughter, J.C.; Flyak, A.I.; Mani, J.; Pauly, M.H.; et al. Efficacy of Human Monoclonal Antibody Monotherapy Against Bundibugyo Virus Infection in Nonhuman Primates. *J. Infect. Dis.* **2018**, *218*, S565–S573. https://doi.org/10.1093/infdis/jiy295.
76. Hastie, K.M.; Salie, Z.L.; Ke, Z.; Halfmann, P.J.; DeWald, L.E.; McArdle, S.; Grinyó, A.; Davidson, E.; Schendel, S.L.; Hariharan, C.; et al. Anti-Ebola virus mAb 3A6 protects highly viremic animals from fatal outcome via binding GP(1,2) in a position elevated from the virion membrane. *Nat. Commun.* **2025**, *16*, 1293. https://doi.org/10.1038/s41467-025-56452-2.
77. Wec, A.Z.; Nyakatura, E.K.; Herbert, A.S.; Howell, K.A.; Holtsberg, F.W.; Bakken, R.R.; Mittler, E.; Christin, J.R.; Shulenin, S.; Jangra, R.K.; et al. A "Trojan horse" bispecific-antibody strategy for broad protection against ebolaviruses. *Science* **2016**, *354*, 350–354. https://doi.org/10.1126/science.aag3267.
78. Fan, P.; Sun, B.; Liu, Z.; Fang, T.; Ren, Y.; Zhao, X.; Song, Z.; Yang, Y.; Li, J.; Yu, C.; et al. A pan-orthoebolavirus neutralizing antibody encoded by mRNA effectively prevents virus infection. *Emerg. Microbes Infect.* **2024**, *13*, 2432366. https://doi.org/10.1080/22221751.2024.2432366.
79. Batista-Duharte, A.; Martínez, D.T.; Carlos, I.Z. Efficacy and safety of immunological adjuvants. Where is the cut-off? *Biomed. Pharmacother.* **2018**, *105*, 616–624. https://doi.org/10.1016/j.biopha.2018.06.026.
80. Furuyama, W.; Shifflett, K.; Feldmann, H.; Marzi, A. The Ebola virus soluble glycoprotein contributes to viral pathogenesis by activating the MAP kinase signaling pathway. *PLoS Pathog.* **2021**, *17*, e1009937. https://doi.org/10.1371/journal.ppat.1009937.
81. Pallesen, J.; Murin, C.D.; De Val, N.; Cottrell, C.A.; Hastie, K.M.; Turner, H.L.; Fusco, M.L.; Flyak, A.I.; Zeitlin, L.; Crowe, J.E.; et al. Structures of Ebola virus GP and sGP in complex with therapeutic antibodies. *Nat. Microbiol.* **2016**, *1*, 16128. https://doi.org/10.1038/nmicrobiol.2016.128.
82. Mohan, G.S.; Li, W.; Ye, L.; Compans, R.W.; Yang, C. Antigenic Subversion: A Novel Mechanism of Host Immune Evasion by Ebola Virus. *PLoS Pathog.* **2012**, *8*, e1003065. https://doi.org/10.1371/journal.ppat.1003065.
83. Liu, Y.; Ye, L.; Lin, F.; Gomaa, Y.; Flyer, D.; Carrion, R.; Patterson, J.L.; Prausnitz, M.R.; Smith, G.; Glenn, G.; et al. Intradermal Vaccination with Adjuvanted Ebola Virus Soluble Glycoprotein Subunit Vaccine by Microneedle Patches Protects Mice Against Lethal Ebola Virus Challenge. *J. Infect. Dis.* **2018**, *218*, S545–S552. https://doi.org/10.1093/infdis/jiy267.
84. Wahl-Jensen, V.M.; Afanasieva, T.A.; Seebach, J.; Ströher, U.; Feldmann, H.; Schnittler, H.-J. Effects of Ebola Virus Glycoproteins on Endothelial Cell Activation and Barrier Function. *J. Virol.* **2005**, *79*, 10442–10450. https://doi.org/10.1128/jvi.79.16.10442-10450.2005.
85. Lubaki, N.M.; Younan, P.; Santos, R.I.; Meyer, M.; Iampietro, M.; Koup, R.A.; Bukreyev, A. The Ebola Interferon Inhibiting Domains Attenuate and Dysregulate Cell-Mediated Immune Responses. *PLoS Pathog.* **2016**, *12*, e1006031. https://doi.org/10.1371/journal.ppat.1006031.
86. Kindzelskii, A.L.; Yang, Z.Y.; Nabel, G.J.; Todd, R.F.; Petty, H.R. Ebola Virus Secretory Glycoprotein (sGP) Diminishes FcγRIIIB-to-CR3 Proximity on Neutrophils. *J. Immunol.* **2000**, *164*, 953–958. https://doi.org/10.4049/jimmunol.164.2.953.
87. Bradley, J.H.; Harrison, A.; Corey, A.; Gentry, N.; Gregg, R.K. Ebola virus secreted glycoprotein decreases the anti-viral immunity of macrophages in early inflammatory responses. *Cell. Immunol.* **2018**, *324*, 24–32. https://doi.org/10.1016/j.cellimm.2017.11.009.
88. Taniguchi, C.M.; Emanuelli, B.; Kahn, C.R. Critical nodes in signalling pathways: Insights into insulin action. *Nat. Rev. Mol. Cell Biol.* **2006**, *7*, 85–96. https://doi.org/10.1038/nrm1837.
89. Bost, F.; Aouadi, M.; Caron, L.; Binétruy, B. The role of MAPKs in adipocyte differentiation and obesity. *Biochimie* **2005**, *87*, 51–56. https://doi.org/10.1016/j.biochi.2004.10.018.
90. Kjaldgaard, L.; Claude, K.M.; Mukadi-Bamuleka, D.; Kitenge-Omasumbu, R.; Dixit, D.; Edidi-Atani, F.; Kuamfumu, M.M.; Bulabula-Penge, J.; Mambu-Mbika, F.; Tshiani-Mbaya, O.; et al. Virus kinetics and biochemical derangements among children with Ebolavirus disease. *eClinicalMedicine* **2022**, *53*, 101638. https://doi.org/10.1016/j.eclinm.2022.101638.
91. Houweling, M.; Vaartjes, W.J.; Van Golde, L.M.G. Metabolic responsiveness to phorbol ester and activity of protein kinase C in isolated hepatocytes from partially hepatectomized rats. *Biochem. Biophys. Res. Commun.* **1989**, *158*, 294–301. https://doi.org/10.1016/S0006-291X(89)80211-6.

92. Volchkova, V.A.; Dolnik, O.; Martinez, M.J.; Reynard, O.; Volchkov, V.E. RNA Editing of the GP Gene of Ebola Virus is an Important Pathogenicity Factor. *J. Infect. Dis.* **2015**, *212*, S226–S233. https://doi.org/10.1093/infdis/jiv309.
93. Hoenen, T.; Marzi, A.; Scott, D.P.; Feldmann, F.; Callison, J.; Safronetz, D.; Ebihara, H.; Feldmann, H. Soluble Glycoprotein Is Not Required for Ebola Virus Virulence in Guinea Pigs. *J. Infect. Dis.* **2015**, *212*, S242–S246. https://doi.org/10.1093/infdis/jiv111.
94. Warfield, K.L.; Swenson, D.L.; Olinger, G.G.; Kalina, W.V.; Aman, M.J.; Bavari, S. Ebola Virus-like Particle–based Vaccine Protects Nonhuman Primates against Lethal Ebola Virus Challenge. *J. Infect. Dis.* **2007**, *196*, S430–S437. https://doi.org/10.1086/520583.
95. McElroy, A.K.; Akondy, R.S.; Davis, C.W.; Ellebedy, A.H.; Mehta, A.K.; Kraft, C.S.; Lyon, G.M.; Ribner, B.S.; Varkey, J.; Sidney, J.; et al. Human Ebola virus infection results in substantial immune activation. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 4719–4724. https://doi.org/10.1073/pnas.1502619112.
96. Paquin-Proulx, D.; Gunn, B.M.; Alrubayyi, A.; Clark, D.V.; Creegan, M.; Kim, D.; Kibuuka, H.; Millard, M.; Wakabi, S.; Eller, L.A.; et al. Associations between Antibody Fc-Mediated Effector Functions and Long-Term Sequelae in Ebola Virus Survivors. *Front. Immunol.* **2021**, *12*, 682120. https://doi.org/10.3389/fimmu.2021.682120.
97. Liu, Q.; Fan, C.; Li, Q.; Zhou, S.; Huang, W.; Wang, L.; Sun, C.; Wang, M.; Wu, X.; Ma, J.; et al. Antibody-dependent-cellular-cytotoxicity-inducing antibodies significantly affect the post-exposure treatment of Ebola virus infection. *Sci. Rep.* **2017**, *7*, 45552. https://doi.org/10.1038/srep45552.
98. Gong, R.; Xiao, G. Engineered Antibody Variable and Constant Domains as Therapeutic Candidates. *Pharm. Pat. Analyst* **2013**, *2*, 637–646. https://doi.org/10.4155/ppa.13.44.
99. Wang, R.; Zhang, H.; Peng, C.; Shi, J.; Zhang, H.; Gong, R. Identification and Characterization of a Novel Single Domain Antibody Against Ebola Virus. *Virol. Sin.* **2021**, *36*, 1600–1610. https://doi.org/10.1007/s12250-021-00454-z.
100. Bu, F.; Ye, G.; Morsheimer, K.; Mendoza, A.; Turner-Hubbard, H.; Herbst, M.; Spiller, B.; Wadzinski, B.E.; Eaton, B.; Anantpadma, M.; et al. Discovery of Nanosota-EB1 and -EB2 as Novel Nanobody Inhibitors Against Ebola Virus Infection. *PLoS Pathog.* **2024**, *20*, e1012817. https://doi.org/10.1371/journal.ppat.1012817.
101. Wang, M.; Zhang, X.; Li, W.; Yao, Y.; Li, E.; Zhang, B.; Zhou, J.; Liu, S.; Gao, Y.; Zhu, Z.; et al. A highly potent nanobody-based bispecific therapeutic provides broad-spectrum protection against ebolavirus. *Nat. Commun.* **2026**, *17*, 4040. https://doi.org/10.1038/s41467-026-70464-6.
102. Lee, J.H.; Andrabi, R.; Su, C.-Y.; Yasmeen, A.; Julien, J.-P.; Kong, L.; Wu, N.C.; McBride, R.; Sok, D.; Pauthner, M.; et al. A Broadly Neutralizing Antibody Targets the Dynamic HIV Envelope Trimer Apex via a Long, Rigidified, and Anionic β-Hairpin Structure. *Immunity* **2017**, *46*, 690–702. https://doi.org/10.1016/j.immuni.2017.03.017.
103. Thadani, N.N.; Gurev, S.; Notin, P.; Youssef, N.; Rollins, N.J.; Ritter, D.; Sander, C.; Gal, Y.; Marks, D.S. Learning from prepandemic data to forecast viral escape. *Nature* **2023**, *622*, 818–825. https://doi.org/10.1038/s41586-023-06617-0.
104. Brannan, J.M.; He, S.; Howell, K.A.; Prugar, L.I.; Zhu, W.; Vu, H.; Shulenin, S.; Kailasan, S.; Raina, H.; Wong, G.; et al. Post-exposure immunotherapy for two ebolaviruses and Marburg virus in nonhuman primates. *Nat. Commun.* **2019**, *10*, 105. https://doi.org/10.1038/s41467-018-08040-w.
105. Bornholdt, Z.A.; Herbert, A.S.; Mire, C.E.; He, S.; Cross, R.W.; Wec, A.Z.; Abelson, D.M.; Geisbert, J.B.; James, R.M.; Rahim, M.N.; et al. A Two-Antibody Pan-Ebolavirus Cocktail Confers Broad Therapeutic Protection in Ferrets and Nonhuman Primates. *Cell Host Microbe* **2019**, *25*, 49–58.e5. https://doi.org/10.1016/j.chom.2018.12.005.
106. Kugelman, J.R.; Kugelman-Tonos, J.; Ladner, J.T.; Pettit, J.; Keeton, C.M.; Nagle, E.R.; Garcia, K.Y.; Froude, J.W.; Kuehne, A.I.; Kuhn, J.H.; et al. Emergence of Ebola Virus Escape Variants in Infected Nonhuman Primates Treated with the MB-003 Antibody Cocktail. *Cell Rep.* **2015**, *12*, 2111–2120. https://doi.org/10.1016/j.celrep.2015.08.038.
107. Bornholdt, Z.A.; Turner, H.L.; Murin, C.D.; Li, W.; Sok, D.; Souders, C.A.; Piper, A.E.; Goff, A.; Shamblin, J.D.; Wollen, S.E.; et al. Isolation of potent neutralizing antibodies from a survivor of the 2014 Ebola virus outbreak. *Science* **2016**, *351*, 1078–1083. https://doi.org/10.1126/science.aad5788.