Cellular Host Receptors of Arboviruses Causing Hemorrhagic Fever: Scientific Review

Majida Hameed Obaida : Al-Furat Al-Awsat Technical University, Najaf Technical Institute, AL Najaf, Iraq. majida.obaida@atu.edu.iq

Saif Jabbar Yasir: Department of Medical Microbiology, College of Medicine, University of Kufa, Najaf, Iraq. saif.alshehmani@uokufa.edu.iq

DOI: https://doi.org/10.63939/w24zc577

Abstract:

Arboviruses that cause hemorrhagic fever are a wide range of RNA viruses that are mostly spread by insects and other arthropods. How well they interact with certain cellular receptors determines how well they can infect human host cells. Recent research has identified several novel cellular host receptors utilized by different arboviruses to penetrate target cells, a process essential for viral replication and subsequent pathogenesis. The human transferrin receptor 1 (TfR1) is very important for New World clade B arenaviruses, which cause hemorrhagic fevers, to get in. Pathogenic arenaviruses, including Machupo and Junin viruses, exploit human TfR1, whereas closely related nonpathogenic viruses utilize TfR1 orthologs from their natural reservoir hosts. Changes in TfR1 can make it easier or harder for someone to get sick. This means that zoonotic diseases could happen if the host receptor changes.

The glycoproteins Gn and Gc both assist the virus with host cell binding. Entry of CCHFV into cells is mediated by clathrin. Changes in pH and cholesterol level can influence this step. It is also possibly involved in dendritic cell DC-SIGN lectin and host cell nucleolin. Through these interactions, macrophages, dendritic cells, and epithelial cells that are key to viral replication and immune evasion become infected. Different receptor types have been linked with the varied hemorrhagic disease–causing arboviruses, such as dengue virus (DENV), West Nile virus (WNV), and others. Other members of this group include glycosaminoglycans, including heparan sulfate; integrins (e.g., αvβ3 integrin); laminin receptors; and various types of lectins (C-type lectins [DC-SIGN]) or Fc gamma receptors (FcγRs). These receptors edify viral tropism and hemorrhagic

pathogenesis through mediating attachment and incorporation of the viruses into either immune or endothelial cells.

Such viruses have undergone various adaptations that permit spillover and establishment of various illnesses, partly evidencing the complexity between a virus and its cellular host, as evidenced by the specificity or redundancy exhibited by a range of receptor molecules in use. Antivirals that target these newly identified cellular receptors are vital for preventing viruses from entering cells. But their functions as receptors mean that targeting them could trigger unwanted side effects.

Cellular host receptors for arboviruses that cause hemorrhagic fever. These include human transferrin receptor 1 for New World arenaviruses. Examples of entrance receptors for Crimean-Congo Hemorrhagic Fever Virus include clathrin-mediated entry receptor involvement which may involve nucleolin and DC-SIGN. They can be Fc receptors, lectins (c-type and sialic acids), integrins, laminin receptors, glycosaminoglycans among other proteins for flaviviruses and other arboviruses. These discoveries broaden the molecular framework of hemorrhagic fever viral entry and pathogenesis and provide opportunities but also challenges for therapeutic intervention.

Keywords: Arboviruses, hemorrhagic fever, Host Receptors, Arthropod-borne viruses, Arboviruses ligand-receptors.

Introduction:

Arboviruses are a group of viruses whose natural arboreal transmission is mediated by arthropod; they cause severe diseases, including the hemorrhagic fever syndromes that are characterized by fever, bleeding diathesis, and multi-organ involvement. The source of arboviruses must use certain cellular host receptors to be able to infect host cells that need for vaccines and treatments targeting viruses, how do virus cause disease. This review aims to provide an overview of recent findings on novel cellular receptors for hemorrhagic fever arboviruses, highlighting their roles in viral attachment, cell entry and immune modulation during infection in the host. Arthropod-borne infections, which annually afflict millions of people worldwide and are involved in over 17% of infectious diseases, have a profound impact on the emergence of new human pathogens.

Dengue, the most prevalent arboviral disease, results in approximately 90 million cases and about 40,000 deaths a year [**1**]. Emerging arboviruses such as *Phlebovirus riftense* (Rift Valley fever virus), *Alphavirus mayaro* (Mayaro fever virus), *Orthoflavivirus nilense* (West Nile fever virus), *Alphavirus chikungunya* (Chikungunya fever virus), and *Orthoflavivirus encephalitidis* (tick-borne encephalitis virus) have also garnered scientific attention as public health concerns [**2**]. Arboviruses are a diverse group of more than 500 viruses transmitted by arthropod vectors such as mosquitoes and ticks [**3**] present on several continents. In the Southeast Asian region, the presence of *Orthoflavivirus denguei*, or dengue fever virus (DENV), and *Orthoflavivirus japonicum*, or Japanese encephalitis virus (JEV), probably due to anthropogenic actions and geographic changes, is the result of a "spillover" of natural zoonotic pathogens into the human population [**2**,**4**].

Cellular host receptors of arboviruses, specifically those causing hemorrhagic fever:

New World clade B arenaviruses known to cause hemorrhagic fever in humans utilize human TfR1 for cell entry. TfR1 is a cellular receptor involved in iron uptake and is highly significant in viral replication and pathogenesis of hemorrhagic fever viruses such as Machupo virus (MACV), Junin virus (JUNV), Guanarito virus (GTOV), and Sabia virus (SABV). Nonpathogenic arenaviruses related to hemorrhagic fever viruses use orthologs of TfR1 from their respective natural hosts. This receptor is rapidly endocytosed, expressed on endothelial cells, and upregulated on activated lymphocytes, facilitating viral hemorrhagic fever development **[5]**. Integrins, heterodimeric glycoproteins (e.g., αvβ3 integrin), have been implicated as functional receptors for certain arboviruses including West Nile virus. Laminin receptors (37-67 kDa), including nonintegrin laminin receptors, have been identified as receptors for dengue virus serotypes and tick-borne encephalitis virus (TBEV).

The idea is that in the case of viruses, when they bind to these receptors, they will infect host cells more easily **[6]**. The Crimean-Congo hemorrhagic fever virus (CCHFV) is one of the most dangerous human pathogens worldwide 4, and it can infect human dendritic cells via the dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN), which directly binds viral glycoproteins. The interaction with viral glycoproteins Gn and Gc during the initial stage of viral attachment, which subsequently enhances penetration **[7]**.

However, further studies are required to confirm the role of nucleolin in viral internalization; nevertheless, it has been suggested that CCHFV may utilize this protein as a cell entry factor. Nucleolin is the predominant nucleolar protein. Attachment factors, such as glycosaminoglycans and heparan sulfate (sulfated polysaccharides present on the surface of cells), have been determined to be critical for many arboviruses, including dengue virus. Other molecules, such as alpha-dystroglycan, serve as receptors for several arenaviruses in the Old World and some of those in the New World. Insulin-Responsive Protein 78 (GRP78): Found to bind dengue virus serotype 2 in liver cells **[6]**. variety of host receptors required for hemorrhagic fever arbovirus cell entry, including recent findings on variation in receptor usage between arenaviruses and other flavivirus or bunyavirus agents of hemorrhagic diseases.

Several host receptors have been associated with arbovirus attachment and entering **[7]**. Luciferases are used to express a cloning vector that is only identified by specific enzymes. Such receptors are lectins, integrins, laminin receptors and Fc gamma receptors (FcγRs), among others. Each flavivirus, including dengue, West Nile and yellow fever viruses, needs a specific repertoire of cellular receptors to enter host cells. WNV utilizes the αvβ3 integrin, a key receptor found on endothelial cells to facilitate attachment and internalization through receptormediated endocytosis **[12]**. Many lectins such as DC-SIGN and mannose receptors located on dendritic cells facilitate the attachment and entry of flaviviruses by interacting with the viral envelope glycoproteins **[8]**. Antibody-dependent enhancement (ADE) of infection through FcγRs I, II, and III on immune cells is a major component of dengue pathogenesis. This binds to DENV-antibody complexes, allowing viral entry and replication in monocytes and macrophages. It could develop dangerous disease. In addition to FcγRs, other non-Fcγ receptors that have the potential to trigger ADE have been identified by scientists. Using drugs to potentiate the effects of a disease, it appears, is not the only way. Other viruses such as chikungunya and Ross River are alphaviruses that enter cells via two different types of cellular reception called integrins and laminin. Laminin receptors have been shown to bind Ross River virus, supporting the notion that this virus selects for infected tissues in skeletal muscle and joints **[8]**.

Other examples of arboviruses, such as dengue fever virus, similarly target cytoskeletal proteins involved in cellular motility and replication complex assembly like dynein and myosin. Arboviral infection alters lipid metabolism, immunological signaling, and reactive oxygen species

(ROS) generation in host cells to promote viral replication by impairing the function of host defenses. There are multiple ways in which Wolbachia endosymbionts modulate the cytoskeleton of their mosquito hosts. They inhibit arboviruses from binding to and infecting cells by blocking proteins essential to this process. The virus cannot infect new people consequently **[8]**. The process of arboviruses entering host cells is complex and relies on many different receptors that can differ between virus families as well as cell types. Thanks to the identification of these receptors, scientists now have new tools to treat arboviral infections and an improved understanding of how these viruses make people sick. **[9]**.

Human hemorraghi yellow vfer is associated with the compounds in these systems (viral envelope proteins that facilitate the binding of the cell to the virus, components of the interferon signaling pathway (STAT1, STAT2), innate immune sensors, including TLRs; RIG-I; and MDA5; enhanced cytokines and apoptosis proteins dysregulation to affect immunity maintenance); and T cell populations needed for control as well as causing pathology. The envelope protein is essential for critical viral processes such as replication and interaction with host receptors. To attach and enter cells, flaviviruses such as Dengue virus, Zika virus, West Nile virus and yellow fever bind to a number of receptors including mannose receptors, glycosaminoglycans like heparan sulfate and C-type lectins (DC-SIGN and L-SIGN) **[10]**.

Alphaviruses, including the Chikungunya virus (CHIKV), utilize Mxra8 as an entry receptor that facilitates viral attachment and internalization **[8]**. The Crimean-Congo hemorrhagic fever virus (CCHFV), a bunyavirus, interacts with cellular receptors like DC-SIGN and nucleolin. But its use of receptors is not as clear as that of flaviviruses and alphaviruses **[10]**. Integrins, laminin receptors, and phosphatidylserine receptors from the TIM and TAM families are also thought to be arboviral receptors. They help viruses get into cells by attaching to enveloped viruses that look like apoptotic bodies **[12]**. Arboviruses use mosquito vector cellular proteins like actin, tubulin, and dystroglycan to get into and move around inside the arthropod host **[13]**. MXRA8 for arthritogenic alphaviruses such as CHIKV and LDLRAD3 for VEEV were identified via CRISPR/Cas9 loss-of-function screens. This makes it easier for viruses to get into cells. These receptors help the process of binding and getting inside. Most of the time, this happens through endocytosis that is mediated by clathrin. In this process, the low pH in endosomes changes the shape of E1-E2 glycoproteins, which makes the membranes stick together and RNA come out.

Attachment factors such as heparan sulfate, C-type lectins, and phosphatidylserine receptors (like TIM-1) bring virions to cell surfaces before receptors interact. **[14]**. Important receptors for major arboviruses: Through E1-E2 clefts, MXRA8 connects to CHIKV, MAYV, RRV, ONNV, and SFV. Cryo-EM structures show that Ig-like domains fit into spikes, which makes it easier for the virus to get inside. Knockout mice have fewer infections in their bones and muscles. VEEV needs LDLRAD3 to get into neurons.

In CRISPR screens in N2a cells, it was by far the most successful due to direct binding and absorption. EEE, SFV, and SINV enter cells through VLDLR and ApoER2. Low-density lipoprotein receptors allow for infection in mammalian and avian cells. Other putative candidates remain to be confirmed, e.g. Laminin receptor and NRAMP2 for SINV or PHB1 and CD147 for CHIKV according biochemical assays **[15]**. The molecular basis for replication and entry: Binding of arboviruses to receptors induces endocytosis. Endosomal acidity drives hemifusion and pore formation by destabilizing E2–E1 heterodimers and opening E1 fusion loops. First, the genomic RNA that is released is translated into nonstructural proteins (nsP1-4) in order to assemble a replication complex that generates negative-strand intermediates for both genomic and subgenomic RNAs encoding structural proteins. Then VLPs, or New Virions are made by plasma membrane spikes; E2-E1. **[16]**.

Cell surface molecules used by arboviruses

Primary attachment/lectin receptors (glycan recognition). Many flaviviruses and some alphaviruses present N-linked glycans on envelope proteins that bind C-type lectins on dendritic cells (DC-SIGN/CD209) or related receptors, concentrating virions for productive uptake. **[17]**. **Heparan sulfate proteoglycans (HSPGs).** Electrostatic interactions between basic patches on viral envelope proteins and cell-surface glycosaminoglycans can serve as low-affinity, high-avidity attachment factors that influence tropism and adaptation in cell culture. **[18]**.

Receptors of initial adhesion and lectins recognizing glycogen Dendritic cells (DC-SIGN/CD209) or similar receptors bind N-linked glycans on the envelope proteins of some flaviviruses and certain alphaviruses to condense virions for productive uptake. **[17]**. HSPGs = heparan sulfate proteoglycans Tropism- and adaptation-related factors in cell culture are mediated by the electrostatic contacts between positively charged patches on viral envelope proteins and

negative charge-rich glycosaminoglycans found on cell surfaces. They are low-affinity, high-intensity interactions. **[18].**

Phosphatidylserine (PtdSer) receptors (TIM/TAM families). Enveloped virions can display PtdSer in their membrane; TIM family proteins bind PtdSer directly, while TAM family receptor tyrosine kinases (AXL, TYRO3, MER) bind indirectly through bridging ligands (Gas6/Protein S) and thereby promote viral uptake and immune modulation. **[19]**.

Specific proteinaceous receptors (high-affinity entry receptors). Examples include MXRA8 for arthritogenic alphaviruses (e.g., chikungunya virus), which acts as a bona fide entry receptor with a defined structural interface to the viral E1–E2 spike. **[20]**.

MXRA8 — a structurally characterized alphavirus entry receptor: High-resolution X-ray and cryo-EM studies show the MXRA8 ectodomain comprises **two Ig-like domains** in a strand-swapped, disulfide-stabilized head-to-head arrangement; the molecule is bowed and presents a hinge/stalk critical for engagement. This unusual topology orients MXRA8 to wedge into a cleft on the virion surface. **[20]**. **Binding mode to CHIKV E spike.** MXRA8 binds in the canyon formed between two adjacent E2–E1 heterodimers of a single trimeric spike and also contacts a neighboring spike; two binding modes were observed in immature-like virus-like particles but only the high-affinity mode is seen with mature infectious CHIKV. Key contact residues on both MXRA8 and the viral E protein explain species-specific differences and the effect of viral maturation on receptor accessibility. The structural placement of MXRA8 explains how a single receptor can bridge spikes and influence the geometric constraints of receptor engagement, thereby determining cell tropism and providing a clear target for small-molecule or antibody inhibitors that block the MXRA8–E interface. Structural coordinates and PDB depositions (e.g., PDB 6JO8 and related entries) document the atomic contacts used for inhibitor design. **[20]**.

Phosphatidylserine receptors (TIM/TAM) and "apoptotic mimicry"

System (in general). TIM receptors (TIM-1/-3/-4) can directly recognize and bind to PtdSer in the lipid envelope of many enveloped arboviruses and facilitate virus internalization via a conserved pocket named MILIBS, motif. In contrast, the TAM receptors require bridging ligands (Gas6 or ProS) to interact with viral PtdSer and activate the TAM RTK for uptake and inhibition of local antiviral responses. Beyond facilitating entry, this "apoptotic mimicry" could also dampen

innate signaling**. [19]** Information peculiar to TIM-1. Genetic and molecular studies have shown that TIM-1 is directly involved in dengue virus endocytosis and productive infection. Further studies using different cell lines have shown that productive uptake (or internalization) of the virus requires TIM-1 ubiquitination and illustrates that post-translational modification of a receptor can affect entry efficiency**. [21].**

Lectin receptors (DC-SIGN) and glycan-mediated attachment

DC-SIGN as a model. DC-SIGN (CD209), a C-type lectin on dendritic cells, recognizes high-mannose N-linked glycans on flavivirus E proteins and concentrates virions on the cell surface; this enhances the probability of interacting with secondary entry factors and is important for infection of immature dendritic cells. Structural reconstructions of virions complexed with DC-SIGN fragments illustrate glycan-mediated docking. **[22]**.

Heparan sulfate proteoglycans (HSPGs) and electrostatic attachment

Role and adaptation. HSPGs act as low-specificity attachment factors via electrostatic contacts; clinical and lab strains differ in HSPG usage, and increased HSPG binding is often associated with cell-culture adaptation and altered virulence/tropism. Blocking HSPG interactions can reduce infectivity in endothelial and other target cells. **[18]**.

From attachment to membrane fusion — cellular uptake routes

A unifying model for many arboviruses: (i) low-affinity attachments (HSPG, lectins) concentrate virions; (ii) high-affinity receptors or PtdSer receptors promote clustering and trigger **clathrin-mediated endocytosis** (or alternative endocytic routes depending on virus and cell type); (iii) acidification and conformational changes in viral fusion proteins (class II fusion proteins for flaviviruses and alphaviruses) mediate membrane merger in late endosomes. The specific repertoire of receptors and the receptor's signaling post-binding—such as high AXL kinase activity—can promote continued infection or termination thereof. The number **[23]**.

These are fundamentally important steps that provided great insights into entrance; due to molecular structures of arbovirus receptors (e.g. MXRA8-alphavirus) and mechanistic deconstruction of attachment and uptake (lectin recognition, HSPG binding, PtdSer-receptor driven uptake and RTK participation), we have made a lot of progress on this front already. In conclusion,

while structural and mechanistic findings are key to developing rational antiviral therapies based on receptor inhibition (blockade antibodies, receptor decoys and small molecule inhibitors), a thorough understanding of the physiological role of the receptor and its in vivo environment is paramount for safely translating these discoveries into effective therapies.

Receptor-mediated entry

Attachment factors (heparan sulfate, C-type lectins) concentrate virions at the cell surface but often do not by themselves trigger productive entry. Secondary/entry receptors engage viral surface proteins and induce the conformational changes or signaling required for internalization. The canonical sequence is: attachment → receptor engagement → internalization (commonly clathrin-mediated endocytosis for flaviviruses) → endosomal maturation and low-pH-triggered membrane fusion (for many enveloped arboviruses) → uncoating and genome release. **[24,25]**.

Alphaviruses — a structural receptor paradigm (MXRA8)

Discovery and importance: A genome-wide CRISPR screen identified **MXRA8** (matrix-remodeling associated protein 8), a cell-adhesion-like Ig-superfamily protein, as an entry mediator for arthritogenic alphaviruses (e.g., chikungunya, Mayaro, Ross River, O'nyong-nyong), and blocking MXRA8 reduces infection in cells and animals. **[26]**. Molecular architecture: MXRA8 contains two Ig-like domains connected by a hinge and a membrane proximal stalk. High-resolution crystal and cryo-EM structures of MXRA8 bound to chikungunya virus (CHIKV) envelope glycoprotein E1–E2 show MXRA8 docks into a "canyon" formed between two adjacent E protein protomers on the viral surface, contacting residues on E1 and E2 across two protomers. The receptor-binding footprint spans both Ig domains and the hinge, explaining how a single receptor molecule bridges receptor surface glycans and protein epitopes. **[27,28]**.

Functional consequences: MXRA8 engagement stabilizes a receptor-bound state that promotes virus internalization; mutations in viral E2 or in MXRA8's binding surfaces decrease infectivity or change host specificity. Structural data explain species-specific differences in susceptibility and guide therapeutic strategies (Mxra8-Fc decoy proteins or blocking antibodies). **[24,27,28]**.

Flaviviruses — heterogeneous receptors and phosphatidylserine (PS)-mediated uptake

Proteoglycans and classical lectin receptors: dengue virus (DENV) and related flaviviruses bind dendritic cells via heparan sulfate proteoglycans and DC-SIGN (CD209). Dengue virus increases its capture and may even penetrate target cells more easily via the interaction between binding to the high-mannose glycans on E protein with DC-SIGN. **[29].**

TIM/TAM family and "apoptotic mimicry": Flaviviruses often display or acquire phosphatidylserine (PS) in their viral envelope and exploit host PS receptors (TIM family and TAM receptor tyrosine kinases via Gas6/Protein S bridging) to enhance uptake — a process called apoptotic mimicry. TIM/TAM engagement typically acts as an entry-enhancing pathway rather than an obligate receptor in all cell types, and it can modulate innate immune signaling. **[30]**. AXL and Zika virus — a contested receptor: AXL (a TAM family kinase) was reported to promote Zika virus (ZIKV) infection in some human cell types, but subsequent work showed mixed results — in many primary cell systems AXL behaves as an attachment/immune-modulatory factor rather than an essential entry receptor. The role of AXL varies by cell type, developmental stage and species; some recent data continue to refine this model. **[31]**.

Structural and mechanistic themes across arboviruses

Multivalent, low-affinity to high-avidity: Virions exploit multivalency — arrays of envelope proteins and multivalent glycans — to convert individually weak interactions into high-avidity binding to cell surfaces, permitting reversible "scanning" before productive receptor engagement. **[32,33]**. Receptors often bind quaternary epitopes: Structural reconstructions show many receptors recognize quaternary surfaces that exist only on assembled virions (for example, MXRA8 bridges two adjacent E protomers); this explains why isolated viral subunits or monomeric proteins can fail to recapitulate receptor binding. **[27,28]**. Contact with the receptor can prompt endocytosis directly or assemble particles at high density before they are taken up through constitutive pathways unique to each virus or cell type. Many enveloped arboviruses undergo membrane fusion in response to low endosomal pH or other endosomal cues that promote rearrangement of E1/E2 (alphaviruses) or E glycoprotein (flavivirus). Cryo-EM experiments describe the conformational changes that expose fusion loops and drive membrane merger, which are triggered by electrostatics. **[24]**.

Implications for tropism, pathogenesis and therapeutics

Which cell types a virus infects and the illness manifestations observed are mostly determined by the receptor expression patterns in tissues. For example, alphaviruses infect synovial fibroblasts and MXRA8, while flaviviruses infect dendritic cells and brain progenitors with variable PS-receptor expression. Structural receptor maps explain cross-species tropism and host barriers. **[26,27,33]**. Therapeutic targeting: High-resolution virus–receptor complexes have motivated development of receptor-decoys (e.g., MXRA8-Fc), blocking monoclonal antibodies, and small molecules that interfere with receptor engagement or downstream endocytic pathways. However, the redundancy of attachment factors and cell-type variability means that blocking a single receptor may not fully abrogate infection in all tissues. **[26,27,33]**. Genome-wide CRISPR screens and haploid genetic screens objectively identify host factors necessary for infection (for instance, the discovery of MXRA8). High-throughput proteomics, virus-overlay binding assays, and single-particle cryo-EM facilitate the mapping of contact residues and glycan dependencies. Comparative structural biology of related arboviruses shows that they have similar receptor footprints and unique insertions that change how receptors are used. Ongoing work continues to nominate new receptors for bunyaviruses, orthobunyaviruses and insect-specific arboviruses. **[25,33,24]**.

Molecular-level understanding of arbovirus–receptor interactions has matured from candidate receptor lists to atomic structures that explain tropism, species specificity, and steps of entry. Alphavirus MXRA8 provides a clear structural example of a receptor that binds a quaternary site on the virion; flaviviruses instead use a repertoire of lectins, PS-binding receptors and attachment factors with more cell-type dependence. Continued integration of genetic screens with cryo-EM and cell biology will reveal additional “novel” receptors and clarify which interactions are essential versus accessory — information that is crucial for rational antiviral design. **[26,32]**. pr/E3 occupancy in alphaviruses) modulates receptor site exposure; dynamic structural snapshots of intermediate maturation states will clarify when and how receptors access specific epitopes. Data from the MXRA8 work suggest that maturation affects modes of high and low affinity. the number **[33]**. Different receptor sequences among species generate different vulnerability patterns, and understanding the structural consequences of polymorphisms can aid in performing zoonotic risk assessment and selecting relevant animal models. The number **[34]**. The molecular interactions

between the viral attachment proteins and numerous cellular receptors or attachment factors enable arthropod-borne viruses to infect certain cell types, tissues, and species. All of these aspects are molecular biology: the specificity of the binding, how strong their interaction is going to be and when will eventually determine tropism. The number **[35]**.

Molecular specificity: determinants of receptor recognition

Alphaviruses (such as chikungunya and Mayaro) attach to the host receptor MXRA8 at an interface utilizing the viral E1/E2 glycoprotein complex; two Ig-like extracellular domains on the receptor possess a complementary surface, which imposes high positional specificity while their protein-protein interactions are also well-studied **[36]**. For example, for many flaviviruses (e.g., dengue and Zika), glycans (e.g., heparan sulfate) or C-type lectins (e.g., DC-SIGN) are used to mediate the initial attachment, leading to an increased pool of permissive cells that ultimately expands the apparent tropism. However additional protein receptors may be required for a genuine entry. **[37]**. This simple one-receptor= one-tropism idea gets complicated when different arboviruses use different host factors (i.e., AXL, TIM and TYRO3 group members involved in Zika/dengue interactions). It causes receptor usage dependent on the type of cell. The number **[38]**.

Binding strength shapes entry and tropism

The measured affinities (for e.g. surface plasmon resonance or biolayer interferometry measurements) correlate with the efficiency of virus entry and infectivity in vitro. Increased receptor affinity interactions typically correlate to a reduction in required effective receptor density for entry, and an expanded receptor tropism. the number **[39]**. Glycosylation and affinity modulationGlycosylation from viruses or host receptors can sterically hinder receptor binding or enhance affinity through binding to receptor binding sites. For instance, the infectivity of certain strains of alphaviruses is influenced by the positioning of glycans on their E proteins, which in turn controls the interaction with MXRA8. **[40]**. Host-range barriers include differences in affinity between species and host polymorphisms, which can also occur within breeds (for example bovines with MXRA8 polymorphisms that do not bind chikungunya possess host-range barriers). The number **[41]**.

Tropism: cellular, tissue, and species consequences

Cell type tropism is mediated by the expression of receptors and co-factors. A virus will only infect tissues that possess adequate quantities of a high-affinity receptor in addition to intracellular factors capable of supporting its replication. This explains how receptor expression maps can be used to predict tropism and clinical signs, such as MXRA8 (in skeletal tissues) or AXL (some brain progenitors). **[42]**. Emergence and receptor plasticity. As a process associated with host propensity and emergence, structural plasticity in viral receptor binding proteins (RBPs) allows changes to receptor usage based on selection pressure. This, in turn, enables greater tropism or transmissibility across species. The number **[43]**. Attachment-related factors influence the initial dispersion. Lectin- and heparan sulfate-bound skin or mucosal cells may retain incoming virions, promoting their infection of tissue-resident cells and/or transfer to immune cells that can digest them (e.g. dendritic cells DC). First, it changes how the virus spreads. **[44]**

Techniques that reveal specificity and affinity by experimental means or structural techniques

High-resolution structural biology (those using cryo-EM or x-ray crystallography) has provided exciting opportunities to predict mutational effects on affinity and tropism, as well as aids at mapping interfaces. The number 45. Functional experimental validation of structural observations and quantification of the impact of changes on tropism is carried out using receptor knockout/knock-in cell lines, receptor-blocking antibody neutralization, SPR/BLI binding kinetics, etc. The number **[46]**.

Implications for disease development, monitoring and handling

The prediction of which viruses will have the potential to cross species barriers and just which receptor alterations will confer heightened tropism depends on our ability to map the sequence diversity of viral receptor binding proteins (RBPs) and host receptors across species. The number **[47]**. Therapeutic targeting: Rational antivirals would block the interactions with high-affinity receptors (using small compounds, receptor decoys, or neutralizing antibodies) However, receptor plasticity and redundancy present challenges. The number **[48]**. To survey for new strains and to rationally design receptor-targeted therapies, a molecular understanding of the specificity and affinity of arbovirus-receptor interactions is essential. Thus, the knowledge is required to

enable understanding tropism on cell, tissue and species levels. The best approach for linking differences in a single residue with differences in tropism relevant to epidemiology is to use structural and biophysical techniques, combined with functional virology.

Findings from structural receptor studies: implications for the therapeutic and experimental arena

Smart design of inhibitors: High-resolution structures of receptor-virus complexes (e.g., MXRA8-CHIKV) contains atomic contact networks that can be filled with small molecules, neutralizing antibodies or receptor decoys. And using cryo-EM maps and Protein Data Bank entries, in silico docking, and epitope mapping of neutralizing antibodies are now possible. **[4]**. A comparison of host-directed vs viral-directed approaches: While interference with interactions with host attachment factors (e.g., DC-SIGN, TIM/TAM, HSPG) may mitigate pathway usage and thus reduce risk of escape by the virus, this approach brings concerns regarding safety related to the physiological functions mediated by these receptors (e.g. apoptotic cell clearance). Conversely, virus-directed antibodies that occlude receptor-binding sites (epitope blocking) can be highly specific. **[49]**. Arboviruses (for example, dengue virus [DENV], Zika virus [ZIKV], West Nile virus, chikungunya virus) enter host cells by binding attachment factors and bona-fide entry receptors on susceptible cells; notable receptor families include C-type lectins (e.g., DC-SIGN), phosphatidylserine (PS) binding proteins such as TIM (TIM-1, TIM-4) and TAM receptors (AXL, Tyro3), heat-shock proteins and other cell-surface molecules. Blocking receptor–virus interactions is a validated antiviral strategy for multiple arboviruses. **[50]**.

Therapeutic approaches that target receptors or receptor usage

Blocking antibodies and receptor antagonists

Monoclonal antibodies (mAbs) can neutralize virus by binding viral envelope proteins or by blocking host receptors required for entry. Human and murine mAbs that block viral envelope epitopes have shown cross-neutralizing activity between dengue and Zika in preclinical work, reducing infection and disease in animal models. Antagonistic antibodies directed against host receptors (e.g., anti-AXL) or small-molecule inhibitors may reduce viral entry in vitro. However, host-directed blockade must balance antiviral benefit against physiological roles of the receptor (e.g., AXL in tissue homeostasis). **[50]**.

Soluble receptor decoys and engineered binding traps

Soluble receptor ectodomains or engineered decoy proteins can sequester virus particles preventing interaction with cell-surface receptors. Soluble forms of PS-binding domains or engineered Fc-fusion receptor fragments have been proposed as entry-blocking therapeutics for PS-mediated "apoptotic mimicry" used by flaviviruses. Decoy approaches aim to reduce viral tropism without permanently altering host cells. **[50]**

Oligonucleotide therapies (siRNA, antisense, ribozymes) to downregulate receptor expression

Antisense oligonucleotides and small interfering RNAs (siRNAs) targeting host receptor mRNAs (for example, AXL or TIM family transcripts) can reduce receptor expression and thereby lower susceptibility to infection in cell models. Oligonucleotide therapies face delivery and off-target challenges but provide a modular, sequence-specific way to transiently lower receptor levels in target tissues. **[51]**

CRISPR-based and gene-editing approaches

CRISPR–Cas technologies can be used ex vivo to knock out critical host factors in permissive cell lines (or engineered tissue grafts) to produce virus-resistant cells. In vivo gene editing to remove a widely expressed receptor carries substantial safety and ethical concerns and is not yet clinically feasible, but it remains a powerful research tool to validate receptors as therapeutic targets. **[51]**.

Small-molecule inhibitors and host pathway modulators

Small molecules that alter receptor trafficking (e.g., modifying ubiquitination or endocytosis of TIM receptors) or inhibit receptor tyrosine kinase activity (for TAM receptors) can reduce virus entry and post-entry steps. Repurposed kinase inhibitors have been tested in cell-culture screens; however, specificity and host toxicity are major limiting factors. **[52]**.

Evidence and examples

TIM-1 and dengue: TIM-1 is involved in the endocytosis of the dengue virus. Changing TIM-1 through genetics or drugs makes it harder for the virus to get into cells, which supports

TIM-1 as a potential treatment target. AXL and Zika: AXL was found to be a major way that ZIKV gets into different types of cells, such as skin and neural progenitors. Blocking AXL with antibodies or knocking it down with siRNA lowers ZIKV infection in vitro, but the importance of this in vivo depends on the tissue and model. Alphavirus receptors: Recent discoveries of new protein receptors for alphaviruses and the tick-borne encephalitis virus have opened up more options for therapeutic targets and shown that there are many different types of receptors in arbovirus families. **[53]**.

Aptamers, nanobodies and small binding scaffolds

Aptamers (nucleic-acid ligands) and single-domain antibodies (nanobodies) can be selected to bind viral envelope proteins or host receptors with high affinity, blocking entry. Aptamers have advanced in stability and delivery, and nanobodies offer small size, tissue penetration, and ease of engineering for intranasal or localized delivery. Both modalities are under active preclinical development for flaviviruses and alphaviruses.

Problems with translation

Trade-offs between host functions— Blocking all of the body's receptors at once could be bad because many of them are important for normal body functions (for example, TAM receptors help control the immune system). The best choice is targeted delivery or temporary modulation. **[8]**. Virus redundancy and plasticity—Arboviruses often employ various attachment factors and receptors; obstructing a single receptor may be inadequate if alternative entry pathways are available. Combination strategies, such as direct antivirals and receptor blockade, may be necessary. Delivery and stability: Oligonucleotides, aptamers, and biologics need delivery systems that work well (like nanoparticles and conjugates) to get to the right tissues (like the skin, placenta, and CNS) safely. **[51]**. ADE and immune modulation—For flaviviruses, immune phenomena such as antibody-dependent enhancement make it harder to design therapeutic antibodies. Receptor-targeted therapies should not accidentally make infection worse or mess up immunity. **[50]** A suggested plan for development

Target validation: use CRISPR screens and genetic knockdown in human cells and organoids that are physiologically relevant to find receptors that have a big effect on viral entry and a low risk of harming the host. **[53]**. Choosing a modality: for receptors that work outside of cells, choose soluble decoys, nanobodies, or monoclonal antibodies; for receptors that work inside

cells, think about oligonucleotides or small molecules that change how things move around. Localized delivery: look into topical or intranasal delivery (to the skin or mucosa) for places where arthropods have bitten and optimized carriers for delivering to the placenta or CNS when appropriate (like ZIKV). Confirm preclinical safety in animal models with regards to how receptor blockade affects local or systemic immunological homeostasis and tissue healing, prior to human administration of the agent. A new entry intervention for arboviruses can be developed in combination with direct-acting antivirals and vaccines, focusing on the entry stage of each virus life cycle through host receptors. A successful therapeutic program should be built on careful target validation, modality selection that aligns with receptor biology and delivery methods that minimize host toxicity while blocking key entry routes. With constant progress in receptor structural biology, aptamers, nanobodies, and oligonucleotides we hope that more and more translational developments can be granted.

Conclusion:

For examples of cellular host receptors used by arboviruses that cause hemorrhagic fever upon binding and entry into the cell, as TF receptor 1 (TfR1) in New World clade B arenaviruses such as Machupo or Junin viruses; DC-SIGN and nucleolin for Crimean-Congo Hemorrhagic Fever Virus (CCHFV); and various ones including FcγRs, C-type lectins, integrins such as αvβ3, laminin receptors and glycosaminoglycans such as heparan sulfate for flaviviruses like dengue (DENV), West Nile(VNV) or yellow-fever virus(YFV). These receptors are involved in pH dependent fusion, clathrin endocytosis and attachment. Because they function as a pair, they can engage with many different types of immune cells, endothelial cells and epithelial tissues. This promotes viral replication, evasion of immunity, and hemorrhage.

Structural studies have shown that Alphavirus E1-E2 spikes such as that of the chikungunya virus incorporate MXRA8's Ig-like domains. By contrast, flaviviruses exploit phosphatidylserine receptors (TIM/TAM relatives) to mimic apoptosis and evade innate immunity in the service of low-pH endosomal entry. Receptor expression patterns that dictate cell-type tropism explain disease symptoms such as bleeding, arthritis and encephalitis; mutations or adaptations could encourage zoonotic spillover. Alphaviruses are expressed by MXRA8 in musculoskeletal tissues, and flaviviruses express their mRNAs via DC-SIGN on dendritic cells. Following virion

accumulation, attachment factors such as heparan sulfate proteoglycans mediate transfer of virions to high-affinity receptors for internalization.

Receptors used by viruses and antivirals that target the receptors should also reduce infection in models without much localized damage. Soluble decoys (MXRA8-Fc); blocking antibodies; siRNAs; aptamers; and small-molecule inhibitors disrupting entry interfaces revealed by cryo-EM structures. Moreover, in order to deal with receptor redundancy, and physiological roles (e.g., TAM in homeostasis), viral plasticity, ADE in flaviviruses, etc., we must use tissue-specific delivery; CRISPR-validated targets; and combination therapy. LDLRAD3 is one of several newly discovered receptors for Venezuelan equine encephalitis virus (VEEV) found by continuous genome-wide screenings and proteomics experiments. Organoid models, haploid screening and structural biology advances will help elucidate the influence of maturation, receptor hierarchies and host polymorphisms on emergence. Combining these ideas helps produce safe and efficacious broad-spectrum therapies, receptor decoys and surveillance systems.

References

1. WHO Fact Sheet: Vector-Borne Diseases. Available online: https://www.who.int/news-room/fact-sheets/detail/vector-borne-diseases (accessed on 14 August 2022).
2. Kading, R.C.; Brault, A.C.; Beckham, J.D. Global Perspectives on Arbovirus Outbreaks: A 2020 Snapshot. *Trop. Med. Infect. Dis.* 2020, *5*, 142.
3. Young, P.R. Arboviruses: A Family on the Move. In *Advances in Experimental Medicine and Biology*; Springer: New York, NY, USA, 2018; Volume 1062, pp. 1–10.
4. Young, K.I.; Medwid, J.T.; Azar, S.R.; Hu, R.M.; Drumm, H.; Co, L.L.; Pitts, R.J.; Buenemann, M.; Vasilakis, N.; Perera, D.; et al. Identification of Mosquito Bloodmeals Collected in Diverse Habitats in Malaysian Borneo Using COI Barcoding. *Trop. Med. Infect. Dis.* 2020, *5*, 51.
5. Abraham J, Kwong JA, Albariño CG, Lu JG, Radoshitzky SR, Salazar-Bravo J, et al. Host-Species Transferrin Receptor 1 Orthologs Are Cellular Receptors for Nonpathogenic New World Clade B Arenaviruses. PLoS Pathog. 2009;5(4): e1000358.

6. Rey F, Stiasny K. Biological Transmission of Arboviruses: Reexamination of and New Insights into the Role of Integrin and Laminin Receptors in Viral Entry. Microbes Infect. 2003 Aug;5(10):865-872.

7. Spengler JR, Bergeron É, Rollin PE. Crimean-Congo Hemorrhagic Fever: Tick-Host-Virus Interactions. Viruses. 2017 May 25;9(5): pii: E106.

8. Kaufman SK, Walker C, Niyogi SC. Biological Transmission of Arboviruses: Reexamination of and New Insights into Components, Mechanisms, and Unique Traits as Well as Their Evolutionary Trends. Clin Microbiol Rev. 2005;18(4):608-637.

9. Chotiwan N, Tran TT, Phasouk K, et al. Intracellular Interactions Between Arboviruses and Wolbachia in Aedes aegypti. Front Cell Infect Microbiol. 2021; 11:690087. Published 2021 Jun 22.

10. Huang YJS, Higgs S, Vanlandingham DL. Arbovirus-Mosquito Vector-Host Interactions and the Impact on Transmission and Disease Pathogenesis of Arboviruses. Front Microbiol. 2019; 10:22.

11. Zhang R, Kim AS, Fox JM, Nair S, Basore K, Klimstra WB, et al. Mxra8 is a receptor for multiple arthritogenic alphaviruses. Nature. 2018;557(7706):570-4.

12. Meertens L, Carnec X, Ramdasi R, Guivel-Benhassine F, Lew E, Lemke G, et al. The TIM and TAM families of phosphatidylserine receptors mediate dengue virus entry. Cell Host Microbe. 2012;12(4):544-57.

13. Lu P, Li J, Zhao J, Yan Q, Yang G, Guo X, et al. The dystroglycan receptor is essential for maintaining high Wolbachia density in Aedes aegypti mosquitoes and for arbovirus transmission blockade. PNAS. 2020;117(43):26843-52.

14. Liu J, et al. Insights into mosquito-borne arbovirus receptors. Trends Microbiol. 2024.

15. Zimmerman O, et al. Entry receptors — the gateway to alphavirus infection. J Clin Invest. 2023;133(2): e165307.

16. Reyes JIL, et al. Intracellular Interactions Between Arboviruses and... Front Cell Infect Microbiol. 2021.

17. Song H, Zhao Z, Chai Y, Jin X, Li C, Yuan F, Liu S, Gao Z, Wang H, Song J, Vazquez L, Zhang Y, Tan S, Morel CM, Yan J, Shi Y, Qi J, Gao F, Gao GF. Molecular basis of arthritogenic alphavirus receptor MXRA8 binding to chikungunya virus envelope protein. Cell. 2019;177(7):1714–1724.e12.

18. Artpradit C, et al. Recognition of heparan sulfate by clinical strains of dengue virus. 2013. Available via PubMed Central.

19. Meertens L, Carnec X, Lecoin MP, Ramdasi R, Guivel-Benhassine F, Lew E, Lemke G, Schwartz O, Amara A. The TIM and TAM families of phosphatidylserine receptors mediate dengue virus entry. Cell Host Microbe. 2012;12(4):544–557.

20. Basore K, et al. Cryo-EM structure of chikungunya virus in complex with the Mxra8 receptor. Cell. 2019

21. Dejarnac O, et al. TIM-1 ubiquitination mediates dengue virus entry. Cell Rep. 2018;23(6):1779–1793.

22. Tassaneetrithep B, Burgess TH, Granelli-Piperno A, Trumpfheller C, Finke J, Sun W, Eller MA, Pattanapanyasat K, Sarasombath S, Birx DL, Steinman RM, Schlesinger S, Marovich MA. DC-SIGN (CD209) mediates dengue virus infection of human dendritic cells. J Exp Med. 2003;197(7):823–829.

23. Cruz-Oliveira C, et al. Receptors and routes of dengue virus entry into the host cells. FEMS Microbiol Rev. 2015;39(2):155–170.

24. Swevers L, *et al.* Mechanisms of cell entry by viruses: attachment factors, receptors and endocytosis. *Rev Virol Cell Biol*. 2021.

25. Anwar MN, *et al.* Review: interactions of flaviviruses with cellular receptors. *Clin Microbiol Rev.* 2022.

26. Zhang R, Kim AS, Fox JM, Nair S, Basore K, Klimstra WB, *et al.* MXRA8 is a receptor for multiple arthritogenic alphaviruses. *Nature*. 2018;557(7706):570–4.

27. Song H, Perlman DH, et al. Molecular basis of arthritogenic alphavirus receptor binding (crystal and cryo-EM analyses). *Cell*. 2019.

28. Basore K, et al. Cryo-EM structure of Chikungunya virus in complex with receptor MXRA8. *PLoS / PMC article* (structure and interface analysis). 2019.

29. Perera-Lecoin M, Meertens L, Carnec X, Amara A. Flavivirus entry receptors: an update. *Viruses*. 2013;5(9):3419–44.

30. Laureti M, Morelli M, *et al.* Flavivirus receptors: diversity, identity and cell entry. *Front Immunol.* 2018.

31. Gorshkov K, et al. Zika virus: origins, pathological action and treatment—review. *Front Microbiol.* 2019. (discussion of AXL controversy).

32. Ribeiro-Filho HV, *et al.* Cryo-EM structure of Mayaro virus and implications for MXRA8 binding and receptor recognition. *Nat Commun.* 2021.

33. Liu J, *et al.* Insights into mosquito-borne arbovirus receptors: approaches and recent receptor discoveries. *Wuhan Univ Press / Review* (2024).

34. Zimmerman O, et al. Vertebrate-class-specific binding modes of the alphavirus receptor family (recent structural/evolutionary analysis). Cell. 2023.

35. Liu J, et al. Insights into mosquito-borne arbovirus receptors. *Trends Microbiol*. 2024.

36. Basore K, et al. Cryo-EM structure of Chikungunya virus in complex with the MXRA8 receptor. *Nat Microbiol* (or J Virol/PMC). 2019.

37. Anwar MN, et al. The interactions of flaviviruses with cellular receptors. *Virology*. 2022.

38. Xie S, et al. AXL, an important host factor for DENV and ZIKV: roles in entry. *Front Microbiol*. 2021; (review). Song H, et al. Molecular basis of arthritogenic alphavirus receptor recognition (MXRA8 structures). *Cell*. 2019.

39. Ribeiro-Filho HV, et al. Cryo-EM structure of Mayaro virus (glycan impacts). Nat Commun. 2021. Nature

40. Kim AS, et al. An evolutionary insertion in the MXRA8 receptor affects alphavirus binding. *PLoS Pathog*. 2020.

41. Feng F, et al. Colocalization of Chikungunya virus with its receptor MXRA8 — implications for tropism. J Virol. 2023. journals.asm.org

42. Raju S, et al. Structural basis for plasticity in receptor engagement by an alphavirus RBP. *Cell*. 2025.

43. Eder J, et al. Transmission of Zika by dendritic cell subsets: DC-SIGN and dissemination. *Front Immunol*. 2023. Basore K / Song H structural works and follow-ups. 12- Reviews and methodological studies summarized in Liu J and Frontiers 2024/2025 reviews.

44. Dufloo J, et al. Receptor-binding proteins from animal viruses and host range predictions. *Nat Microbiol*. 2025.

45. Sarukhanyan E, et al. In silico designed AXL receptor blocking drug candidates. *ACS Omega*. 2018.

46. Zimmerman O, et al. Vertebrate-class-specific binding modes of the alphavirus receptor family (recent structural/evolutionary analysis). Cell. 2023. (Discusses species differences in MXRA8 usage.) Lee JK, et al. Advances in Zika Virus–Host Cell Interaction. *Viruses*. 2019;11(5): E567.

47. Panda K, et al. Oligonucleotide-Based Approaches to Inhibit Dengue Virus. *Molecules*. 2021;26(4):956.

48. Dejarnac O, et al. TIM-1 ubiquitination mediates dengue virus entry. *Cell Reports*. 2018

49. Zimmerman O, et al. Entry receptors — the gateway to alphavirus infection. *J Clin Invest*. 2023;133(12): e165307.

50. Camacho-Concha N, et al. Insights into Zika Virus Pathogenesis and Potential Therapeutic Targets. *J Pers Med*. 2023;11(12):3316.

51. Mislan NAL, et al. Aptamer as a therapeutic agent for dengue infections. *[PMC article]* 2025.

52. Camacho-Concha N, et al. Insights into Zika Virus Pathogenesis and Potential Therapeutic Targets. *J Pers Med*. 2023;11(12):3316.

53. Li P, et al. LRP8 is an entry receptor for tick-borne encephalitis viruses. *PNAS*. 2025