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Neuroinvasive Tropism and Molecular Pathogenesis of Rabies Virus: Advanced Prophylactic Interventions, One Health Surveillance, and Future Horizons

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Abstract

Rabies remains one of the most lethal zoonotic neurotropic diseases affecting warm-blooded animals and humans, causing an estimated 59,000 human deaths annually despite being completely preventable. Caused by neurotropic single-stranded negative-sense RNA viruses of the genus *Lyssavirus*, family *Rhabdoviruses*, the Rabies Virus (RABV) displays an unprecedented ability to evade host innate immune responses and selectively invade the central nervous system (CNS). This technical review evaluates the molecular architecture and life cycle of RABV, retrograde axonal transport dynamics, host-pathogen interactions, and neuroinvasive pathophysiology. Furthermore, it discusses state-of-the-art diagnostic platforms, modern Cell Culture and Embryonated Egg Vaccines (CCEEVs), recombinant monoclonal antibody (mAb) cocktails, and post-exposure prophylaxis (PEP) protocols. Finally, we highlight systemic control strategies under the global "One Health" framework—specifically mass dog vaccination, oral rabies vaccination (ORV) in wildlife reservoirs—and outline future horizons including mRNA-based rabies vaccines, novel pan-lyssavirus therapeutic antibodies, and gene-editing platforms targeting viral replication.

1. Introduction and Aetiology

Rabies is an acute, progressive, and almost uniformly fatal viral encephalomyelitis. The causative pathogen, Rabies Virus (RABV), is the prototypical member of the genus *Lyssavirus* within the family *Rhabdoviridae* (Yousaf et al., 2012). Morphologically, RABV virions are bullet-shaped particles measuring approximately 180 nm in length and 75 nm in diameter, possessing a

non-segmented, negative-sense single-stranded RNA genome of approximately 11.9 kilobases (Davis *et al*., 2015).

1.1 Structural Architecture and Components of Rabies Virus (RABV) Virion

1.1.1 General Morphology & Genome Characteristics:

• Shape: Distinctive bullet-shaped cylindrical geometry (~180 nm length × 75 nm diameter).

• Genome: Non-segmented, negative-sense, single-stranded RNA (-ssRNA) of ~11.9 kilobases (kb).

• Gene Order (3' to 5'): 3' - N - P - M - G - L - 5'

• Virion Mass: Consists of a host-derived lipid envelope with embedded glycoprotein trimer spikes, enclosing a tightly packaged ribonucleoprotein (RNP) core.

Table 1: Molecular Architecture and Functional Roles of RABV Virion Structural Components

Component	Virion Location	Structural Properties	Primary Biological / Pathogenic Role
Glycoprotein (G)	Spike / Surface Envelope	Trimeric transmembrane spikes (outer surface)	• Mediates host viral receptor attachment (nAChR, NCAM, p75NTR). • Facilitates low-pH endosomal membrane fusion. • Primary immunogen eliciting Virus-Neutralizing Antibodies (VNAs).
Matrix Protein (M)	Inner Envelope / Shell	Layer between RNP core and lipid bilayer	• Maintains structural integrity and bullet-shaped virion morphology. • Regulates viral assembly and membrane budding via host interactions. • Modulates host innate immune response and transcription shut-off.

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Component	Virion Location	Structural Properties	Primary Biological / Pathogenic Role
Nucleoprotein (N)	Ribonucleoprotein (RNP) Core	Encapsidates negative-sense genomic RNA	• Forms a ribonuclease-resistant helical RNP complex. • Essential template for transcription and genomic replication. • Primary target antigen for diagnostic identification (FAT / dRIT).
Phosphoprotein (P)	Ribonucleoprotein (RNP) Core	Cofactor non-catalytic subunit bound to L & N	• Essential non-catalytic cofactor for RdRp (L protein) activity. • Binds dynein light chain (LC8) for retrograde axonal transport. • Blocks host Type I IFN pathways by inhibiting STAT1/STAT2 signaling.
Large Protein (L)	Ribonucleoprotein (RNP) Core	Low abundance viral RNA polymerase	• Multifunctional viral RNA-dependent RNA Polymerase (RdRp). • Executes transcription, replication, 5' capping, and 3' polyadenylation. • Drives replication cascade within Negri bodies inside host neurons.

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Component	Virion Location	Structural Properties	Primary Biological / Pathogenic Role
Lipid Bilayer Envelope	Outer Membrane	Host cell membrane derivative	• Lipid envelope acquired during viral budding through host cell plasma membrane. • Confers structural vulnerability to lipid solvents, detergents, heat, and desiccation.

The genome encodes five structural proteins arranged in a conserved sequence (3′−N−P−M−G−L−5′):

1. **Nucleoprotein (N):** Encapsidates viral RNA, forming a ribonuclease-resistant helical ribonucleoprotein (RNP) complex essential for transcription and replication (Yousaf *et al*., 2012).
2. **Phosphoprotein (P):** Acts as a non-catalytic cofactor for the viral RNA-dependent RNA polymerase (L) and plays a pivotal role in blocking host interferon signalling pathways (Dietzschold *et al*., 2008).
3. **Matrix Protein (M):** Regulates virion assembly, drives budding from the host plasma membrane, and facilitates structural integrity (Yousaf *et al*., 2012).
4. **Glycoprotein (G):** Forms trimeric surface spikes that mediate host cell receptor binding, clathrin-mediated endocytosis, and low-pH membrane fusion, acting as the primary target for virus-neutralizing antibodies (VNAs) (Davis *et al*., 2015; Natesan *et al*., 2023).
5. **Large Protein / RNA-Dependent RNA Polymerase (L):** Mediates transcription, replication, capping, polyadenylation, and phosphorylation functions (Yousaf *et al*., 2012).

2. Molecular Pathogenesis and Neuroinvasion

2.1 Peripheral Entry and Receptor Interaction

Transmission typically occurs via transdermal inoculation of infectious saliva through the bite or scratch of a rabid mammal. Following entry into muscular or sub-epithelial tissue, RABV binds to specific surface receptors on peripheral nerve terminals or neuromuscular junctions (NMJs) (Davis *et al*., 2015). Key host cell entry receptors include:

- **Nicotinic Acetylcholine Receptor (nAChR):** Exclusively located at the postsynaptic muscle membrane (Davis *et al*., 2015).

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- **Neural Cell Adhesion Molecule (NCAM / CD56):** Expressed widely across neuronal membranes (Dietzschold *et al*., 2008).
- **Low-Affinity Nerve Growth Factor Receptor (p75NTR):** Facilitates viral uptake into sensory and motor axon terminals (Davis *et al*., 2015).

Inoculation via Rabid Bite ---> Local Viral Replication in Muscle Cells (Optional Phase) ---> Binding to Receptors (nAChR, NCAM, p75NTR) at Neuromuscular Junction ---> Internalization & Retrograde Axonal Transport via Dynein Motors (3–100 mm/day) ---> Entry into Spinal Cord & Brainstem (Rostral Spread) ---> Rapid Widespread Encephalitis & Centrifugal Spread to Salivary Glands

2.2 Axonal Retrograde Transport and CNS Invasion

Upon receptor-mediated endocytosis, intact virions or nucleocapsids are internalized into endosomal vesicles. RABV interacts directly with the host dynein motor complex via the viral Phosphoprotein (P), enabling fast retrograde axonal transport along microtubules toward the soma of primary sensory or motor neurons at speeds ranging from 3 to 100 mm per day (Dietzschold et al., 2008; Davis et al., 2015).

Once the virus reaches the dorsal root ganglia or ventral horn of the spinal cord, rapid trans-synaptic spread occurs. RABV spreads centripetally to the brainstem, thalamus, basal ganglia, and cerebral cortex.

2.3 Immune Evasion and Neurodegeneration

Remarkably, RABV preserves neuronal structural integrity during early-to-mid stages of infection to maintain the host neural architecture required for viral dissemination (Davis et al., 2015). RABV evades host immunity through multiple molecular mechanisms:

- The **P protein** inhibits STAT1/STAT2 nuclear translocation, directly blocking Type I and Type II interferon-mediated antiviral cascades (Dietzschold *et al*., 2008).
- Upregulation of immunosuppressive molecules (such as FasL and HLA-G / PD-L1) induces apoptosis in invading virus-reactive T-lymphocytes.
- Inhibition of caspase-3 activation prevents premature apoptosis of infected neurons.

Subsequent neurological dysfunction stems from synaptic impairment, mitochondrial dysfunction, altered neurotransmitter release (acetylcholine, GABA, serotonin), and reactive microgliosis, culminating in clinical manifestations of encephalitic ("furious") or paralytic ("dumb") rabies (Dietzschold et al., 2008). In the terminal phase, centrifugal spread via anterograde transport delivers the virus to innervated peripheral organs, most notably the acinar cells of the salivary glands for transmissible shedding (Davis et al., 2015).

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3. Clinical Spectrum and Diagnostic Methodologies

Diagnostic Platform	Target / Biomarker	Sensitivity / Specificity	Clinical Utility
Fluorescent Antibody Test (FAT)	Viral Nucleoprotein (N) Antigen in fresh brain tissue	Gold Standard (Sensitivity: >98%)	Post-mortem confirmation in suspected animal/human cases
Direct Rapid Immunohistochemical Test (dRIT)	Viral Nucleoprotein (N) Antigen in brain tissue	Equivalent to FAT (High field specificity)	Post-mortem surveillance in low-resource/field settings
Reverse Transcription Polymerase Chain Reaction (RT-qPCR)	Viral RNA (N or L gene regions)	High sensitivity (>99%)	Antemortem (nuchal biopsy, saliva, CSF) and molecular epidemiology
Rapid Fluorescent Focus Inhibition Test (RFFIT)	Virus Neutralizing Antibody (VNA) titers	Standard for serology (≥0.5 IU/mL)	Post-vaccination immunity testing

4. Control, Prophylaxis, and Prevention Strategies

Post-Exposure Prophylaxis (PEP) must be initiated immediately following potential exposure (Category II and Category III bites/scratches according to WHO criteria). PEP is virtually 100% effective in preventing clinical onset when administered correctly prior to symptom development (Natesan et al., 2023).

Component	Clinical Execution Protocol	Target Group / Indication
1. Local Wound Management	Thorough, continuous flushing and washing of all bite wounds and scratches with clean running water, soap, and virucidal agents (70% ethanol or povidone-iodine) for at least 15 minutes. Primary suturing should be strictly delayed.	Mandatory for all Category I (if skin broken), II, and III exposures immediately post-incident.

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Component	Clinical Execution Protocol	Target Group / Indication
2. Passive Immunization	Local infiltration of Rabies Immunoglobulin (HRIG at 20 IU/kg or ERIG at 40 IU/kg) or Recombinant Monoclonal Antibodies (e.g., Twinrab, Rabishield) into and around all wound margins. Any remaining volume is injected intramuscularly at a site distant from the vaccine.	Category III exposures (single or multiple transdermal bites/scratches, licks on broken skin, or mucous membrane contamination).
3. Active Immunization (Intradermal Regimen)	**WHO IPC Schedule:** 2×0.1 mL intradermal injections administered at two distinct anatomical sites (e.g., left and right deltoids) on Days 0, 3, 7, and 28.	Category II and III exposures (reduces vaccine volume by 60–80% compared to IM regimens).
4. Active Immunization (Intramuscular Regimen)	**Essen Schedule:** Single 0.5 mL or 1.0 mL dose administered intramuscularly in the deltoid muscle (adults) or anterolateral thigh (young children) on Days 0, 3, 7, 14, and 28. *(Gluteal administration is strictly contraindicated).*	Category II and III exposures (standard alternative when intradermal administration is unavailable

4.1 Local Wound Management

Immediate, thorough washing of all wound sites with clean running water, soap, and virucidal agents (e.g., 70% ethanol or povidone-iodine) for at least 15 minutes physically reduces viral load at the inoculation site by up to 90% (Yousaf et al., 2012). Primary suturing of wounds should be strictly delayed; if unavoidable, passive immunoglobulins must be infiltrated beforehand.

4.2 Passive Immunization: RIGs and Monoclonal Antibodies

For Category III exposures (single or multiple transdermal bites/scratches, mucous membrane contamination), passive rabies immunoglobulins (RIG) provide immediate virus-neutralizing antibodies before active vaccine-induced immunity develops:

- **Human Rabies Immune Globulin (HRIG):** Administered at 20 IU/kg body weight.
- **Equine Rabies Immune Globulin (ERIG):** Administered at 40 IU/kg body weight.
- **Recombinant Human Monoclonal Antibody Cocktails (mAbs):** Modern biological alternatives (e.g., Rabishield, Twinrab, SYN023) offer standardized efficacy, reduced

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batch-to-batch variation, lower production costs, and zero risk of adventitious animal pathogens (Chao et al., 2020).

The full calculated dose of RIG or mAb cocktail must be infiltrated locally into and around all wound margins. Any remaining volume should be injected intramuscularly at a site distant from the vaccine administration site.

4.3 Active Immunization Protocols

Modern Cell Culture and Embryonated Egg Vaccines (CCEEVs)—such as Purified Vero Cell Rabies Vaccine (PVRV) and Purified Chick Embryo Cell Vaccine (PCECV)—have entirely superseded older tissue-derived vaccines:

- **Intradermal (ID) Regimens (WHO IPC Schedule):** 2×0.1 mL injections on Days 0, 3, 7, and 28. This regimen reduces overall vaccine volume requirements by 60–80%, making it highly cost-effective for endemic regions (Kewcharoenwong et al., 2024).
- **Intramuscular (IM) Regimens (Essen Schedule):** Single 0.5 mL or 1.0 mL dose administered on Days 0, 3, 7, 14, and 28 in the deltoid muscle (adults) or anterolateral thigh (young children); gluteal administration is contraindicated due to reduced immunogenicity.

5.0 One Health Framework and Global Elimination

- Under the global target "Zero by 30" established by WHO, WOAH, FAO, and GARC, elimination of human deaths from dog-mediated rabies requires systemic implementation of the **One Health** paradigm (Wirblich *et al*., 2017):

  Mass Canine Vaccination (≥70% coverage of domestic dog populations to establish herd immunity) ---> Wildlife Oral Rabies Vaccination (ORV baiting programs targeting wild carnivore reservoirs) ---> Integrated Bite Case Management (IBCM uniting veterinary surveillance, animal quarantine, and human post-exposure prophylaxis) ---> Community Engagement and Responsible Dog Ownership Programs ---> Inter-Sectoral Data Sharing and Disease Surveillance ---> Interruption of Animal-to-Human Transmission and Achievement of Global Dog-Mediated Rabies Elimination ("Zero by 30")

- **Component 1: Mass Canine Vaccination (MDV)** — Sustained mass immunization targeting ≥70% of free-roaming and domestic dog populations to break the primary transmission cycle.

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- **Component 2: Wildlife Oral Rabies Vaccination (ORV)** — Deployment of oral vaccine baits in sylvatic habitats to control viral circulation in wildlife reservoirs (e.g., foxes, raccoons, skunks, jackals).
- **Component 3: Integrated Bite Case Management (IBCM)** — Joint operational protocols linking human medical facilities and veterinary departments for real-time bite reporting, animal tracking/quarantine, and risk-based PEP administration.
- **Component 4: Inter-Sectoral Surveillance & Policy** — Unified cross-departmental data exchange, laboratory capacity building, public awareness campaigns, and policy integration to achieve the global "Zero by 30" mandate.

6.0 Future Horizons and Emerging Innovations

- **mRNA-Based Rabies Vaccines:** mRNA platforms encoding the full-length RABV Glycoprotein (G) packaged in lipid nanoparticles (LNPs) demonstrate rapid, robust, and durable neutralizing antibody responses with reduced dose requirements and simplified manufacturing profiles (Natesan et al., 2023).
- **Broadly Neutralizing Pan-Lyssavirus Monoclonal Antibodies:** Next-generation mAb cocktails designed to bind highly conserved epitopes on the G protein aim to provide cross-neutralizing protection against non-RABV phylogroup I and II lyssaviruses (e.g., Mokola, Lagos bat, Duvenhage, European bat lyssaviruses) (Chao et al., 2020).
- **Gene Editing and Antiviral Interventions:** CRISPR-Cas platforms targeting conserved viral RNA regions (N and L genes) along with novel small-molecule inhibitors targeting Dynein-P protein interactions represent promising avenues to interrupt early axonal transport.
- **Nanoparticle-Mediated Drug Delivery across the Blood-Brain Barrier (BBB):** Developing brain-penetrating functionalized liposomal and polymeric nanocarriers loaded with therapeutic neutralizing antibodies or antivirals offers potential avenues for treating clinically overt rabies cases, historically considered incurable.

7.0 Conclusion

Rabies remains a classic model of neurotropic viral pathogenesis, leveraging sophisticated molecular strategies to access and devastate the central nervous system. Although clinical rabies carries an unmatched fatality rate, complete prevention is achievable through immediate wound care, timely administration of modern cell culture vaccines, and prompt local infiltration of monoclonal antibodies or immunoglobulins. Realizing the global mandate to eliminate human

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deaths from dog-mediated rabies by 2030 requires sustained commitment to the One Health framework—uniting mass canine immunization campaigns, oral wildlife vaccination, advanced diagnostics, and equitable access to post-exposure biologics.

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