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Development of Antiviral Therapies for Feline Infectious Diseases

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Abstract Feline infectious diseases, caused by various viral pathogens such as Feline Leukemia Virus (FeLV), Feline Immunodeficiency Virus (FIV), and Feline Infectious Peritonitis Virus (FIPV), pose significant health challenges to domestic and wild cats. This study explores the current state of antiviral therapy development for these diseases, delving into the mechanisms of viral replication and host interactions, the efficacy and limitations of existing antiviral treatments, and emerging therapeutic approaches. These include targeting viral proteins, host-directed therapies, gene editing, and broad-spectrum antiviral drugs. A case study focusing on the development of GS-441524 for FIP highlights the successes and challenges of implementing new therapies. The study also discusses the importance of personalized medicine, the potential of combination therapies, and strategies to combat drug resistance. This research underscores the importance of continued innovation and collaboration in veterinary medicine to improve outcomes for cats affected by viral diseases.

Keywords Feline infectious diseases; Antiviral therapy; Feline leukemia virus (FeLV); Feline immunodeficiency virus (FIV); Feline infectious peritonitis (FIP); Veterinary medicine

1 Introduction

Feline infectious diseases, caused by a range of viral pathogens, pose significant health threats to domestic and wild cat populations. Common feline viruses such as Feline Leukemia Virus (FeLV), Feline Immunodeficiency Virus (FIV), and Feline Infectious Peritonitis (FIP) have been of particular concern due to their high prevalence and the severe morbidity and mortality they induce. These diseases not only affect the health and well-being of individual cats but also have broader implications for feline populations, complicating efforts in breeding, sheltering, and conservation (Cook et al., 2020; Jones et al., 2021; Roy et al., 2022). The complexity of these viral infections, coupled with the limited therapeutic options currently available, underscores the urgent need for novel antiviral interventions (Catella et al., 2021).

The development of effective antiviral therapies for feline infectious diseases is critical for improving the prognosis and quality of life for affected cats. While vaccines have been somewhat successful in preventing certain infections, many viruses continue to evade immune defenses, leading to chronic and often fatal conditions (Bergmann et al., 2019; Delaplace et al., 2021). The current treatment landscape is limited, with most therapies focusing on managing symptoms rather than directly targeting the viral pathogens. Effective antiviral treatments would not only help in reducing the viral load in infected cats but could also potentially prevent the spread of these diseases within cat populations, thus mitigating the impact on feline health globally (Takano et al., 2019; Cook et al., 2021).

This study examines the current state of antiviral therapy development for feline infectious diseases, highlighting recent advancements, ongoing challenges, and future opportunities in the field. It provides a detailed analysis of the mechanisms of action of existing antiviral drugs, explores potential novel therapeutic targets, and evaluates the feasibility of translating emerging treatments from human medicine to veterinary applications. This comprehensive overview aims to guide future research efforts, emphasizing the importance of innovation and collaboration to develop effective, safe, and accessible antiviral therapies that address the unique needs of feline infectious diseases.

2 Overview of Feline Infectious Diseases

2.1 Common feline viral infections

Feline infectious diseases encompass a variety of viral pathogens that significantly impact the health of domestic and wild cats. Two of the most common and severe viral infections are Feline Leukemia Virus (FeLV) and Feline Immunodeficiency Virus (FIV). FeLV is a retrovirus that primarily affects the immune system, leading to immunosuppression, anemia, and lymphoma in infected cats (Hofmann-Lehmann and Hartmann, 2020). FIV, another retrovirus, similarly compromises the immune system, making infected cats more susceptible to secondary infections and chronic diseases (Fedorov et al., 2021). Both viruses are transmitted primarily through close contact, such as biting or grooming, making them highly prevalent among outdoor and feral cat populations (Kokkinaki et al., 2021).

2.2 Pathogenesis and clinical manifestations

The pathogenesis of FeLV and FIV is complex and varies based on the stage of infection and the immune response of the host. FeLV infection can lead to a range of outcomes, from asymptomatic carriers to severe disease manifestations such as lymphoma, bone marrow suppression, and immunosuppression (Duda et al., 2020). Infected cats may develop progressive, regressive, or abortive infections, with progressive infections leading to the most severe outcomes, including persistent viremia and early death (Fusco et al., 2023).

FIV infection typically progresses through three stages: an acute phase characterized by mild, nonspecific symptoms such as fever and lymphadenopathy; a long subclinical phase; and a terminal phase, where the cat becomes highly susceptible to opportunistic infections and neoplasms due to severe immunosuppression. Clinical signs of FIV include chronic gingivostomatitis, weight loss, chronic infections, and neurologic disorders.

2.3 Current challenges in managing feline viral infections

Managing FeLV and FIV infections presents significant challenges due to the chronic nature of these diseases and the lack of curative treatments. Diagnosis can be difficult, particularly in the early stages of infection when viral loads may be low and clinical signs are nonspecific (Hofmann-Lehmann et al., 2018). Moreover, the potential for latent infections and the reactivation of viremia complicates the clinical management of infected cats, as ongoing monitoring and supportive care are often required.

Treatment options are limited, focusing primarily on managing symptoms and preventing secondary infections rather than eliminating the virus. Antiviral therapies, such as reverse transcriptase inhibitors, have been explored, but their efficacy is limited and they are often cost-prohibitive (Kostiuk et al., 2019). The development of effective vaccines has also been challenging due to the high variability of viral strains and the complex interactions between the virus and the host immune system (Little et al., 2020). As a result, prevention through vaccination, routine testing, and managing exposure to infected cats remains the cornerstone of controlling the spread of these viral infections.

3 Mechanisms of Viral Replication and Host Interaction

3.1 Understanding viral life cycles in cats

The replication cycles of feline viruses, such as Feline Leukemia Virus (FeLV) and Feline Immunodeficiency Virus (FIV), are intricate processes that enable these pathogens to persist in their feline hosts. These retroviruses follow a life cycle that includes attachment to host cells, reverse transcription of their RNA genomes into DNA, integration into the host genome, and subsequent production of viral particles. Upon entering a host cell, these viruses hijack the cellular machinery to replicate their genetic material and produce new viral particles, leading to persistent infections (Colpitts et al., 2020). Feline Calicivirus (FCV), another common feline pathogen, also utilizes the host's translational machinery to produce viral proteins while degrading host mRNA to ensure its replication is prioritized (Figure 1) (Wu et al., 2021).

3.2 Host-virus interactions and immune response

Host-virus interactions are critical in determining the outcome of viral infections. When a feline virus infects a host, it triggers an immune response designed to eliminate the virus. The innate immune system is the first line of

defense, with pattern recognition receptors (PRRs) detecting viral components such as RNA or DNA. This detection leads to the production of type I interferons and other cytokines that initiate an antiviral state in the host (Kasuga et al., 2021). For example, Feline Herpesvirus (FHV-1) induces type I interferon signaling as part of the host's response to viral infection, but this response is often counteracted by the virus itself, leading to persistent infection (Tian et al., 2018). The adaptive immune system, involving T cells and B cells, further enhances the host's ability to control and eventually clear the infection, though many feline viruses have evolved mechanisms to evade these immune responses.

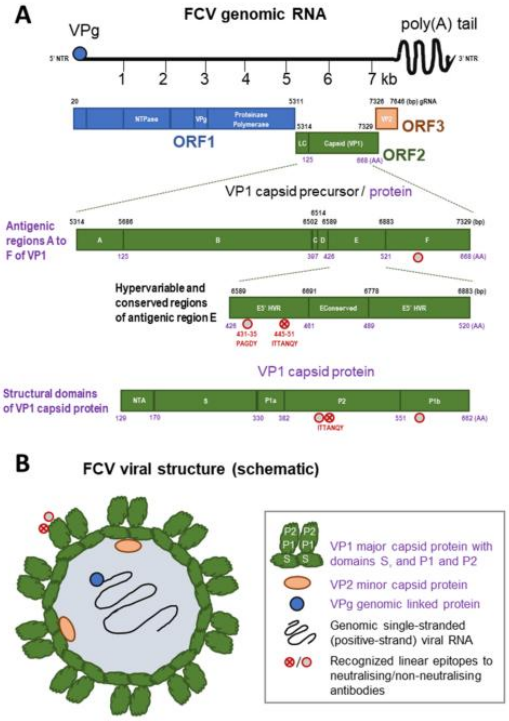

Figure 1 Genomic Organization of Feline Calicivirus (FCV) and Antigenic Regions of Its Major Proteins (Adapted from Hofmann-Lehmann et al., 2022)

Image caption: The figure illustrates the open reading frames (ORF1, ORF2, and ORF3) of the viral RNA, along with the various encoded proteins, including VP1 and VP2. The VP1 protein contains multiple antigenic regions (A through F), with region E further divided into subregions with high variability and conserved sequences. The diagram also details the N-terminal arm (NTA), shell (S), and protruding (P) domains of the VP1 protein. This figure aids in understanding how the structural and antigenic variations of FCV influence the virus's immune evasion mechanisms and its infection process within host cells (Adapted from Hofmann-Lehmann et al., 2022).

3.3 Mechanisms of viral evasion of host defenses

Feline viruses have developed sophisticated strategies to evade host immune defenses, ensuring their survival and persistence within the host. For instance, FHV-1 employs the US3 protein to inhibit type I interferon signaling by preventing the dimerization of Interferon Regulatory Factor 3 (IRF3), a key player in the antiviral response (Tian et al., 2018).

Tian et al. (2018) investigated how the US3 protein of Feline Herpesvirus 1 (FHV-1) employs a novel immune evasion mechanism to block the host's type I interferon signaling pathway. The study demonstrated that the US3 protein effectively inhibits interferon production by preventing the dimerization of interferon regulatory factor 3 (IRF3) in a manner independent of its kinase activity (Figure 2). Through both in vivo and in vitro experiments, researchers found that recombinant viruses lacking the US3 gene induced greater interferon production compared to wild-type viruses, significantly reducing the virus's pathogenicity. Additionally, the absence of US3 prevented the virus from invading the trigeminal ganglia, indicating that US3 plays a critical role in FHV-1 neurovirulence and the establishment of latent infection. This research not only uncovers a new mechanism by which FHV-1 evades the host immune response but also provides new insights into the virus's persistent infection in cats.

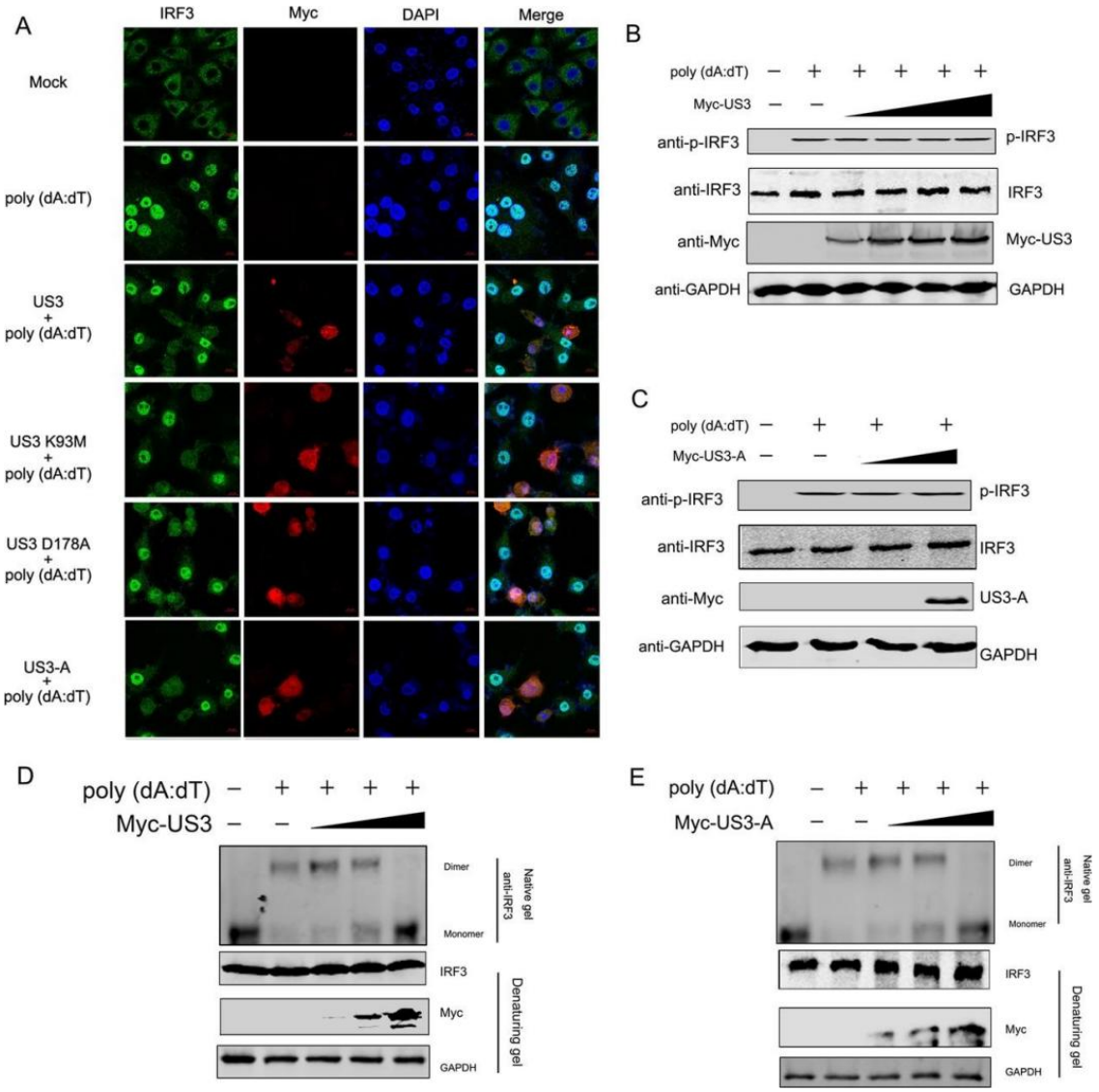

Figure 2 Mechanism by Which US3 Protein Blocks the Interferon Signaling Pathway by Inhibiting IRF3 Dimerization (Adapted from Tian et al., 2018)

Image caption: Cell localization experiments revealed that US3 effectively inhibits the stimulus-induced translocation of IRF3 to the nucleus. Although US3 does not affect the phosphorylation levels of IRF3, it significantly reduces the formation of IRF3 dimers. The experiments also showed that the N-terminal region of US3 (amino acids 1-75) has the same effect as the full-length US3 in inhibiting IRF3 dimerization. These findings suggest that US3 interferes with IRF3 dimerization, thereby suppressing the production of type I interferon, which helps FHV-1 evade the host's immune response (Adapted from Tian et al., 2018)

Similarly, viruses like FeLV can modulate host DNA methylation patterns to suppress immune responses, thereby avoiding detection and destruction by the immune system (Kuss-Duerkop et al., 2018). Another strategy involves the manipulation of host microRNAs (miRNAs), such as miR-26a, which can enhance viral survival by promoting type I interferon signaling inhibition during FHV-1 infection (Zhang et al., 2019).

4 Current Antiviral Therapies for Feline Infectious Diseases

4.1 Antiviral drugs: classes and mechanisms of action

The current landscape of antiviral drugs for feline infectious diseases primarily includes nucleoside analogs, protease inhibitors, and natural compounds. Nucleoside analogs, such as GS-441524, function by incorporating themselves into viral RNA during replication, leading to premature termination of viral genome synthesis. This class of drugs has shown significant efficacy against Feline Infectious Peritonitis Virus (FIPV), a variant of feline coronavirus responsible for Feline Infectious Peritonitis (FIP) (Cook et al., 2021). Protease inhibitors, such as GC376, target the viral proteases required for processing viral polyproteins into functional proteins, thereby

inhibiting viral replication (Perera et al., 2018). Additionally, natural compounds like Thymus vulgaris essential oil have shown virucidal activity against FIPV, offering a complementary approach to synthetic drugs (Catella et al., 2021).

4.2 Existing treatments: efficacy and limitations

Despite the availability of some antiviral drugs for feline viral infections, their efficacy is often limited, and they come with significant challenges. For instance, while GS-441524 has been effective in treating FIP, it is not yet officially approved for veterinary use, which limits its availability and increases the risk of black-market versions of the drug (Izes et al., 2020). Moreover, protease inhibitors like GC376, though promising, have shown varying degrees of success depending on the viral strain and the stage of the infection (Cook et al., 2022). Additionally, the use of natural antivirals, while beneficial in vitro, often lacks the necessary pharmacokinetic data to support their widespread adoption in clinical settings (Bergmann et al., 2019).

4.3 Emerging antiviral agents: potential and challenges

Emerging antiviral agents hold promise for more effective treatments of feline infectious diseases, but they also face significant hurdles. Novel compounds like molnupiravir and its derivatives are currently being explored for their potential to inhibit feline coronaviruses, showing promising results in early studies (Cook et al., 2022). These emerging therapies, however, must overcome challenges such as drug resistance, the need for extensive clinical trials, and regulatory approvals before they can be widely used in veterinary medicine. Moreover, the development of combination therapies that target multiple stages of the viral life cycle may offer more comprehensive protection against these diseases, but they require careful optimization to avoid adverse interactions and ensure synergistic effects (Wagoner et al., 2022).

5 Novel Approaches in Antiviral Therapy Development

5.1 Targeting viral proteins and enzymes

One of the primary strategies in antiviral therapy development is directly targeting viral proteins and enzymes essential for viral replication and survival. This approach includes the development of direct-acting antiviral agents (DAAs) that inhibit viral enzymes such as proteases and polymerases. For example, protease inhibitors targeting the 3C-like protease (3CLpro) of coronaviruses have shown significant efficacy in blocking viral replication, including in feline coronaviruses responsible for Feline Infectious Peritonitis (FIP) (Perera et al., 2018). Additionally, advancements in targeting viral genomes, such as using CRISPR/Cas systems to degrade viral RNA, represent a promising area of research for developing broad-spectrum antiviral agents (Hoang et al., 2022).

5.2 Host-targeted therapies: modulating the immune response

Host-targeted therapies (HTAs) focus on modulating the host’s immune response to enhance antiviral defenses. These therapies aim to inhibit viral replication by targeting host proteins and pathways that viruses hijack for their replication. By targeting host factors, HTAs can offer broad-spectrum antiviral activity and reduce the likelihood of resistance development. For instance, inhibitors of host dihydroorotate dehydrogenase (DHODH), an enzyme critical for pyrimidine biosynthesis, have shown promise as broad-spectrum antiviral agents by limiting viral replication while simultaneously enhancing immune responses (Zheng et al., 2022). Moreover, modulating interferon pathways, which are central to the antiviral immune response, is another potential strategy for enhancing the host's defense mechanisms against various viral infections (Yuan et al., 2020).

5.3 Gene editing and RNA interference approaches

Gene editing technologies, such as CRISPR/Cas9, and RNA interference (RNAi) strategies represent innovative approaches to directly target and disable viral genomes within infected cells. CRISPR/Cas9 can be engineered to target and cut specific viral DNA or RNA sequences, effectively neutralizing the virus's ability to replicate (Hoang et al., 2022). Similarly, RNAi can be used to silence viral genes by introducing small interfering RNAs (siRNAs) that degrade viral RNA transcripts, preventing the production of essential viral proteins. These techniques are still in the early stages of development for veterinary use but hold great potential for the treatment of persistent viral infections in cats.

5.4 Development of broad-spectrum antiviral agents

The development of broad-spectrum antiviral agents (BSAAs) that can target a wide range of viruses is crucial in the fight against emerging and re-emerging viral pathogens. BSAAs work by targeting conserved host pathways or viral components that are critical across multiple virus families. For instance, targeting viral entry mechanisms, such as clathrin-mediated endocytosis, can inhibit the infection of various viruses, including feline viruses (Mazzon et al., 2019). Additionally, broad-spectrum peptides that disrupt viral envelopes have shown efficacy against a wide array of enveloped viruses, offering a versatile tool in antiviral therapy (Cho, 2018). The continued research and development of BSAAs will play a pivotal role in preparing for and mitigating future viral outbreaks in both human and veterinary medicine (Wang et al., 2022; Barua et al., 2023).

6 Case Study

6.1 Case study in antiviral therapy development for feline coronavirus

The development of antiviral therapies for Feline Infectious Peritonitis (FIP), a fatal disease caused by feline coronavirus, serves as a significant case study in veterinary medicine. FIP arises from a mutation in the feline enteric coronavirus (FECV), leading to a highly virulent form of the virus that is difficult to treat. One of the most promising antiviral therapies developed for FIP is GS-441524, a nucleoside analog that inhibits viral RNA-dependent RNA polymerase, effectively halting viral replication. The compound demonstrated substantial success in clinical settings, where it significantly improved survival rates among cats diagnosed with FIP (Jones et al., 2021).

Additionally, combination therapies have been explored to enhance treatment efficacy. For instance, combining GS-441524 with protease inhibitors like GC376 has shown promising results in vitro, suggesting that targeting multiple stages of the viral life cycle can lead to synergistic antiviral effects (Cook et al., 2021). These therapies have expanded the potential for managing FIP, offering hope where previously there were limited options.

6.2 Successes and challenges in the implementation of new therapies

The successful development and implementation of GS-441524 and related antiviral therapies have been met with significant achievements, notably the increased survival rates of cats suffering from FIP. However, these successes are accompanied by several challenges. One major issue is the lack of regulatory approval for GS-441524, which has led to its use through unlicensed channels, often at high costs and with potential risks associated with the quality and consistency of the drug (Delaplace et al., 2021). Another challenge is the emergence of drug-resistant viral strains, which can occur due to the selective pressure exerted by these antiviral agents. This resistance can undermine the efficacy of treatments and necessitate the development of new or combination therapies to overcome it (Agostini et al., 2018).

Moreover, logistical and financial barriers remain a significant concern, especially for pet owners who may struggle with the high costs associated with long-term antiviral treatment. The administration of these drugs, often requiring injections over several weeks, can also be challenging and stressful for both the cat and the owner.

6.3 Lessons learned and implications for future research

The case of FIP treatment underscores the importance of a multifaceted approach in antiviral drug development. The use of combination therapies, targeting different aspects of the viral life cycle, has proven to be a key strategy in enhancing treatment efficacy and preventing the development of resistance. This approach suggests that future research should focus on the identification and development of additional antiviral agents that can be used in combination with existing treatments to improve outcomes.

Another lesson is the critical need for regulatory frameworks that can expedite the approval and distribution of effective antiviral therapies in veterinary medicine. The challenges faced by owners in accessing GS-441524 highlight the importance of ensuring that life-saving treatments are both accessible and affordable.

Furthermore, the development of antiviral therapies for FIP has implications for broader coronavirus research, including the treatment of human coronaviruses such as SARS-CoV-2. The cross-applicability of antiviral

strategies between animal and human medicine provides valuable insights into the mechanisms of viral replication and the potential for broad-spectrum antiviral agents (Cook et al., 2020).

7 Evaluating the Safety and Efficacy of Antiviral Therapies

7.1 Preclinical testing: in vitro and in vivo models

Preclinical testing is a crucial step in the development of antiviral therapies, allowing researchers to evaluate the safety and efficacy of potential treatments before advancing to clinical trials. In vitro models, such as cell cultures, are used to assess the antiviral activity of compounds against specific viruses. These models allow for the screening of large numbers of compounds and the identification of those with potent antiviral effects. For example, studies have used in vitro systems to evaluate the efficacy of various antiviral agents against Feline Infectious Peritonitis Virus (FIPV), identifying promising candidates like GS-441524 and remdesivir (Cook et al., 2021). In vivo models, typically involving animal studies, further assess the pharmacokinetics, toxicity, and therapeutic potential of these compounds in a living organism. These studies are essential for understanding the potential side effects and therapeutic windows of antiviral agents before they are tested in humans or companion animals like cats.

7.2 Clinical trials: methodologies and challenges

Clinical trials are the cornerstone of evaluating the safety and efficacy of antiviral therapies in the target population. These trials are typically conducted in phases, starting with Phase I trials that assess safety in a small group of healthy volunteers or patients, followed by Phase II and III trials that evaluate efficacy and further monitor safety in larger groups. Conducting clinical trials for feline antiviral therapies presents unique challenges, including the recruitment of a sufficient number of participants, managing variations in disease presentation, and ensuring the ethical treatment of animal subjects (Singh et al., 2022). Additionally, the placebo effect can be difficult to measure in veterinary trials, and the variability in how pets are cared for outside of the clinical setting can impact the consistency of trial results (Gbinigie et al., 2023). Despite these challenges, well-designed clinical trials are essential for determining the real-world efficacy of antiviral therapies and for gaining regulatory approval for their use.

7.3 Safety profiles: adverse effects and long-term implications

Understanding the safety profiles of antiviral therapies is critical, especially for treatments intended for chronic use or for vulnerable populations such as young or immunocompromised animals. Adverse effects can range from mild reactions, such as gastrointestinal upset, to more severe outcomes, including organ toxicity or immunosuppression. For example, antiviral agents like remdesivir and GS-441524 have been associated with varying levels of hepatotoxicity and nephrotoxicity, which require careful monitoring during treatment (Cook et al., 2021). Long-term implications of antiviral use also need to be considered, particularly the risk of developing drug resistance, which can render treatments less effective over time (Helou and Razonable, 2019). Ongoing post-marketing surveillance and additional long-term studies are essential to fully understand the safety and efficacy of these therapies in real-world settings.

8 Future Directions in Feline Antiviral Research

8.1 Identification of new therapeutic targets

The future of antiviral therapy for feline infectious diseases lies in the identification of novel therapeutic targets that can more effectively disrupt viral replication and survival. Advances in genomics and proteomics have provided insights into viral-host interactions, identifying host dependency factors that are essential for viral replication. These factors, such as host enzymes involved in the viral life cycle, represent promising targets for new antiviral drugs. For example, targeting viral RNA polymerase and proteases, as well as host factors like cyclophilins, has shown potential in the development of new antiviral strategies (Xu et al., 2021; Badia et al., 2022).

8.2 Personalized medicine approaches

Personalized medicine, which tailors medical treatment to the individual characteristics of each patient, is a growing field in human medicine and holds promise for veterinary applications as well. In feline antiviral therapy,

personalized approaches could involve tailoring treatment plans based on the specific viral strain involved, the cat's genetic makeup, and its immune status. For instance, genomic sequencing of viral strains could guide the selection of the most effective antiviral agents, while pharmacogenomics could optimize drug dosing to minimize adverse effects and maximize efficacy (Pizzorno et al., 2018).

8.3 Potential for vaccine development and combined therapies

Vaccine development remains a critical area of research in the prevention of feline infectious diseases. The development of vaccines that target conserved viral epitopes across different strains could provide broad protection and reduce the reliance on antiviral drugs. Furthermore, the combination of antiviral therapy with vaccination strategies could enhance treatment outcomes, especially in cases where the virus has already established infection. Recent advancements in epitope prediction and molecular docking techniques have enabled the design of multi-epitope vaccines, which show promise in eliciting robust immune responses (Shah et al., 2020).

8.4 Addressing drug resistance in feline viral pathogens

The emergence of drug-resistant viral strains is a significant challenge in the management of infectious diseases. To combat this, future research must focus on developing antiviral agents that are less prone to resistance. This can be achieved through strategies such as drug repurposing, targeting multiple stages of the viral life cycle, and designing drugs that exploit conserved viral structures. For instance, the use of broad-spectrum antivirals and the exploration of host-targeted therapies are promising approaches to mitigating the risk of resistance (Ma et al., 2021).

The continuous advancement in antiviral research, including the identification of new targets, the adoption of personalized medicine, the development of vaccines, and strategies to overcome drug resistance, will shape the future of effective feline antiviral therapies (Takano et al., 2020).

9 Concluding Remarks

The development of antiviral therapies for feline infectious diseases has made significant strides, particularly with the advent of compounds like GS-441524 and remdesivir, which have shown efficacy in treating Feline Infectious Peritonitis (FIP). The exploration of novel therapeutic targets, such as viral enzymes and host dependency factors, has opened new avenues for antiviral drug development. Furthermore, the integration of personalized medicine approaches and the potential for combined therapies, including vaccination, represent promising strategies to enhance treatment outcomes and prevent disease spread. Despite these advancements, challenges remain, particularly in addressing drug resistance and ensuring the safety and efficacy of new antiviral agents across diverse feline populations.

The progress in feline antiviral therapy has significant implications for veterinary medicine, particularly in improving the prognosis and quality of life for cats affected by viral diseases. The successful development and application of antiviral therapies not only provide veterinarians with more effective tools for managing conditions like FIP but also set the stage for the broader application of these therapies to other feline viral infections. The potential for personalized treatment approaches, informed by genetic and immunological profiling, could lead to more targeted and effective interventions, reducing the trial-and-error approach that often characterizes current veterinary practices. Moreover, the integration of antiviral therapies with vaccination strategies could play a crucial role in the prevention and management of infectious diseases in feline populations.

To continue advancing the field of feline antiviral therapies, several key areas require further exploration. First, ongoing research should focus on the identification and validation of new therapeutic targets, particularly those that are less likely to develop resistance. This includes both viral and host targets, with an emphasis on understanding the mechanisms of action and potential off-target effects. Second, the adoption of personalized medicine in veterinary practice should be prioritized, with the development of diagnostic tools that can guide treatment decisions based on the individual characteristics of each cat. Third, the safety and long-term efficacy of new antiviral therapies need to be rigorously tested in diverse feline populations, including those with underlying

health conditions. Finally, there is a need for enhanced collaboration between researchers, veterinarians, and regulatory bodies to ensure that new therapies are accessible, affordable, and widely adopted in clinical practice. By addressing these areas, the field can continue to evolve, ultimately leading to better outcomes for cats affected by viral diseases.

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Conflict of Interest Disclosure

The authors affirm that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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