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Review Article

Decoding Nature's Disease-Tolerance Toolkit: Comparative Immunobiology of Large Mammals, Pathogen–Host Interactions and Translational Opportunities for Human Medicine

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ABSTRACT

Large mammals represent a valuable yet comparatively underexplored source of biological information for understanding the mechanisms that determine disease resistance, disease tolerance, immune-mediated tissue injury, and survival. Unlike conventional laboratory models, large mammals exhibit distinctive physiological, immunological, metabolic, and evolutionary adaptations that can substantially influence host–pathogen interactions. This review provides a comprehensive comparative perspective on the biological mechanisms underlying lethal disease in large mammals, with particular emphasis on the interaction between pathogen virulence, innate and adaptive immunity, inflammatory signalling, cellular stress, regulated cell death, tissue injury, and systemic organ dysfunction. Major disease models, including bovine leukemia virus, African swine fever, bovine respiratory disease, chronic wasting disease, foot-and-mouth disease, hemorrhagic septicemia, and bovine tuberculosis, are considered to illustrate distinct patterns of persistent infection, acute systemic inflammation, immune evasion, immunosuppression, neurodegeneration, and immunopathology. The review further examines species-specific immune adaptations, highlighting elephants as models of enhanced tumour surveillance, camelids as unique sources of heavy-chain-only antibodies and nanobody technologies, and bats as important models for understanding antiviral resistance and disease tolerance. Particular emphasis is placed on the emerging concept that survival depends not only on pathogen elimination but also on the ability of the host to limit collateral tissue damage during infection. Collectively, comparative immunology of large mammals provides an evolution-inspired framework for discovering mechanisms of disease resistance and tolerance and translating naturally evolved biological solutions into innovative strategies for infectious disease, inflammatory disorders, and cancer research.

Introduction

Infectious diseases remain a major challenge to animal health, biodiversity, food security and global public health. Their clinical outcome is not determined solely by the intrinsic virulence of a pathogen; rather, disease severity emerges from a dynamic interaction among pathogen replication, host immune responses, tissue-specific susceptibility, cellular stress responses, metabolic adaptation and environmental factors. The uploaded thesis emphasizes this pathogen–host "tug-of-war" as a central determinant of disease progression and highlights the importance of comparing immune responses across mammalian species to understand why apparently similar infections can produce markedly different outcomes. Contemporary comparative immunology increasingly supports this concept, demonstrating that large and agricultural animals can reveal immunological processes that are difficult to reproduce in conventional laboratory rodents and can provide clinically relevant information concerning infectious diseases, vaccines, antibody responses and immunotherapies [1].

Large mammals occupy a particularly informative position within comparative biology because their prolonged lifespan, complex physiology, diverse ecological niches and substantial body size impose distinctive evolutionary pressures on host defence. Elephants, horses, camels, cattle, rhinoceroses and other large mammals have evolved immune architectures that permit them to maintain tissue integrity and physiological homeostasis while continuously confronting environmental pathogens. The thesis identifies elephants, horses, camels, rhinoceroses and other megafauna as important examples in which species-specific immune adaptations may contribute to differential disease susceptibility, resistance or tolerance. Rather than considering immunity simply as an antimicrobial weapon, comparative immunology increasingly recognizes immunity as a regulated system that must simultaneously eliminate pathogens, restrict excessive inflammation and preserve host tissues. This distinction between resistance and tolerance provides an important conceptual framework for understanding lethal disease. Resistance refers primarily to mechanisms that reduce pathogen burden, whereas tolerance describes mechanisms that limit tissue damage and maintain host function despite persistent or substantial pathogen burden. A host may therefore survive an infection not because it completely eliminates the pathogen, but because it prevents uncontrolled inflammation, oxidative damage, inappropriate cell death and organ dysfunction. This principle is particularly evident in bats, several species of which can maintain high levels of viral replication or exposure while exhibiting comparatively limited clinical disease. Recent reviews indicate that bat antiviral biology involves complementary adaptations that enhance antiviral readiness while restraining inflammatory pathology, providing an important natural model of disease tolerance [2].

The immune system represents a major determinant of this balance. Innate immunity provides rapid recognition of pathogen-associated molecular patterns through pattern-recognition receptors, followed by activation of macrophages, neutrophils, dendritic cells, interferon pathways, complement and inflammatory mediators. Adaptive immunity subsequently provides antigen-specific responses through B and T lymphocytes, antibody production, cytotoxicity and immunological memory. The thesis describes these two arms as complementary components of host defence and emphasizes the contribution of macrophages, dendritic cells, B lymphocytes and T lymphocytes to pathogen control and immune regulation. However, excessive or persistent activation of these pathways may transform a protective response into immunopathology. Hyperinflammation, cytokine dysregulation, uncontrolled inflammatory cell death and tissue injury can therefore become important contributors to mortality during otherwise controllable infections. The thesis similarly identifies excessive inflammatory responses, apoptosis, necroptosis and other regulated cell-death mechanisms as important determinants of disease outcome [3].

This immunological balance is particularly relevant to viral zoonoses. Bats represent a striking example of a host that can tolerate numerous viruses with limited clinical manifestations, whereas infection with related or similar pathogens may produce severe inflammatory disease in humans and other susceptible hosts. The thesis discusses bat-associated Hendra virus, Nipah virus, Marburg virus, Kasokero virus, influenza A virus and coronaviruses, emphasizing the diversity of viral agents associated with different bat species. Importantly, the document describes constitutive or rapidly inducible antiviral interferon responses together with restrained inflammatory signalling as potential mechanisms contributing to viral tolerance. Recent evidence further indicates that regulation of

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inflammasome activation, inflammatory cell death, oxidative stress and DNA damage may contribute to the ability of bats to control viral infection while minimizing tissue injury [4].

The relevance of such adaptations extends beyond understanding bat biology. Viral emergence increasingly occurs at interfaces among humans, animals and ecosystems, making comparative host immunity an important component of One Health and pandemic preparedness. Contemporary One Health research emphasizes that animal hosts should not simply be regarded as passive reservoirs; their immune, ecological and physiological characteristics can influence pathogen persistence, transmission, host switching and disease emergence. Accordingly, understanding why some hosts tolerate potentially lethal pathogens while others develop severe immunopathology may provide opportunities for identifying host-directed strategies to reduce disease severity [5].

Large mammals also offer important insights into non-infectious biological problems associated with immunity, tissue maintenance and cancer. The evolutionary problem known as Peto's paradox is particularly relevant to large, long-lived species: theoretically, greater body size and longevity should increase the probability of malignant transformation, yet cancer risk does not increase proportionally across mammals. Elephants are especially interesting because expansion of the TP53 retrogene family has been proposed as one component of their unusual cancer-protective biology. The thesis similarly identifies enhanced tumour suppression involving TP53 as a distinctive feature of elephants. Although the precise contribution of individual TP53-related mechanisms remains an active area of investigation, elephant biology illustrates how comparative studies can identify naturally evolved strategies for maintaining genomic integrity and controlling damaged cells.

Another striking example of evolutionary innovation is provided by camelids. Unlike conventional mammalian antibodies, camelids produce functional heavy-chain-only antibodies whose antigen-binding domains can exist as compact single-domain structures. These variable heavy-chain domains, commonly termed VHHs or nanobodies, combine antigen specificity with small molecular size, stability and considerable engineering flexibility. The thesis identifies camelid heavy-chain antibodies as a major species-specific immune adaptation and highlights their potential biomedical significance. The translational importance of this phenomenon has expanded substantially, with camelid-derived single-domain antibodies now being investigated and developed for diagnostic, imaging and therapeutic applications; recent literature reports multiple VHH-containing therapeutics that have obtained regulatory authorization. Thus, comparative immunology can move beyond descriptive biology toward the discovery of molecular platforms with direct pharmaceutical potential [6].

Large-animal species are consequently becoming increasingly valuable as complementary models for biomedical research. Their anatomy, physiology, immune responses and naturally occurring diseases can more closely reproduce selected aspects of human biology than conventional small-animal systems. Large-animal models have been used to investigate infectious diseases, vaccine responses, antibody production, transplantation, cancer and immunotherapy, while naturally occurring diseases in livestock and companion animals can generate clinically relevant hypotheses for human medicine. This does not imply that large mammals are universally superior to rodents; rather, model selection should be guided by the biological question, pathogen, immune mechanism and translational endpoint under investigation [7-8].

An additional dimension is the study of immune evasion versus immune regulation. Successful pathogens have evolved mechanisms capable of suppressing interferon signalling, modifying antigen presentation, manipulating apoptosis and altering inflammatory pathways. The thesis specifically identifies interferon suppression, reduced antigen presentation, apoptosis induction and chronic immune activation among mechanisms through which pathogens may weaken host defence and promote disease progression. Understanding these mechanisms alongside host-specific counteradaptations may reveal why the same pathogen can produce asymptomatic infection in one species but severe or fatal disease in another. This comparative approach may therefore identify host pathways that are sufficiently conserved to become therapeutic targets while simultaneously revealing species-specific adaptations that could inspire novel drug, antibody or vaccine technologies [9].

The therapeutic implications of comparative immunobiology are particularly important in an era in which conventional pathogen-directed approaches face challenges from antimicrobial resistance, viral evolution, immune escape and unpredictable zoonotic emergence. Host-directed therapies, immune modulators, engineered antibodies, nanobodies, vaccines and precision immunotherapies could potentially benefit from mechanisms discovered in naturally disease-tolerant species. The thesis already identifies host-directed strategies, immunotherapy,

checkpoint modulation and camelid antibody technology as emerging translational avenues. Recent work similarly emphasizes preventive immunology, advanced vaccines, monoclonal antibodies, nanovaccines, cytokine modulation and other approaches within a One Health framework.

Despite increasing knowledge, important gaps remain. Immune responses are highly heterogeneous among species and even among populations of the same species. Much of the existing literature remains fragmented across veterinary immunology, virology, evolutionary biology, oncology and human medicine. Furthermore, the term "large mammal" encompasses animals with profoundly different evolutionary histories and immune architectures; therefore, apparent similarities should not automatically be interpreted as conserved mechanisms. The thesis itself recognizes species variation in immune efficiency, inflammatory responses and pathogen tolerance as an important determinant of disease susceptibility and outcome. Integrating these differences into a mechanistic comparative framework is essential for avoiding overgeneralization and for translating observations from one species into meaningful biomedical hypotheses.

Against this background, the present review adopts a disease-tolerance-centered comparative immunobiological perspective. Rather than merely cataloguing lethal diseases affecting large mammals, it examines how pathogen characteristics interact with innate and adaptive immunity, inflammatory signalling, regulated cell death, oxidative stress, genomic maintenance and species-specific immune adaptations to determine disease outcome. Particular emphasis is placed on the contrasting biological strategies represented by elephants, camelids and bats, while considering other large mammals as important comparative and translational systems. The review further explores how naturally evolved mechanisms of pathogen resistance and tissue protection can inform vaccine development, antibody engineering, host-directed therapies, immunomodulation, diagnostics and pandemic preparedness.

Ultimately, comparative immunology provides an opportunity to view lethal disease not simply as a consequence of pathogen aggression but as an outcome of the interaction between pathogen burden, immune resistance, immune tolerance and tissue resilience. The thesis concludes that understanding these interactions can contribute to improved vaccines, diagnostics, immunotherapies and disease-prevention strategies in both veterinary and human medicine. The emerging literature strengthens this perspective by demonstrating that large-animal immunology can provide unique insights into infectious disease, antibody biology, vaccine development and therapeutic intervention. A systematic decoding of these naturally evolved "disease-tolerance toolkits" may therefore provide a productive bridge between comparative biology and next-generation translational medicine [10,11].

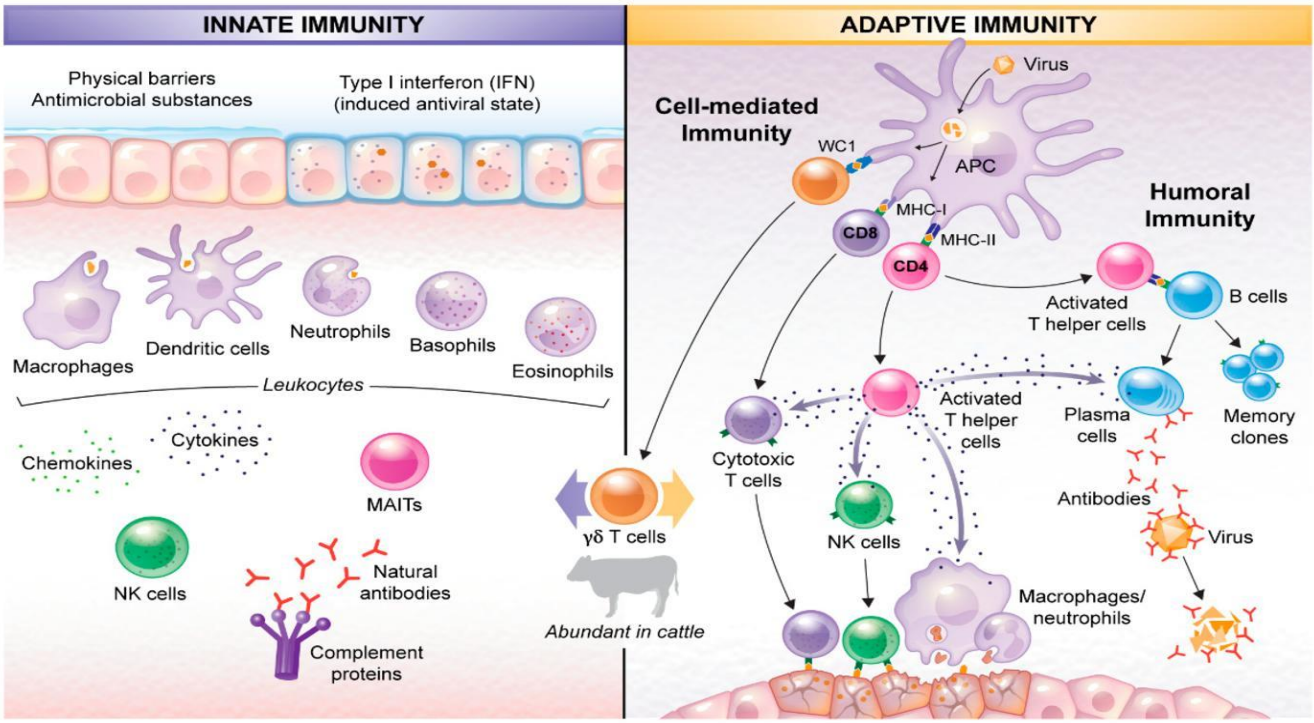

Figure 1: Comparative Immunology and Disease Survival in Large Mammals.

Comparative Immunology of Large Mammals: From Conserved Defence to Species-Specific Adaptation

The immune system of mammals is built around a broadly conserved architecture comprising innate and adaptive components; however, the functional characteristics, cellular composition, receptor repertoires and regulatory mechanisms of immunity can vary substantially among species. Historically, immunological research has relied heavily on laboratory rodents because of their low maintenance cost, short generation time, extensive genetic resources and availability of experimental reagents. Nevertheless, important differences between rodent and human immunity limit the extent to which findings obtained from conventional small-animal models can always be extrapolated to human disease. Large and agricultural mammals—including cattle, horses, pigs, sheep, goats, camels and other species—can provide complementary information because of their distinctive physiology, immune organization, lifespan and naturally occurring diseases. A recent comprehensive review emphasized that large-animal models can contribute uniquely to understanding infectious disease, antibody responses, vaccine development, transplantation and immunotherapies [12].

The thesis similarly emphasizes that large mammals possess specialized immune mechanisms that enable them to resist, tolerate or survive potentially lethal diseases. These mechanisms involve both innate and adaptive immunity, together with species-specific adaptations that influence inflammatory responses, pathogen clearance, tissue injury and disease outcome. Thus, comparative immunology should not be viewed merely as an extension of conventional animal experimentation. Rather, it provides an evolutionary framework for identifying naturally optimized biological strategies that have developed under different ecological, metabolic and pathogen-selection pressures.

Innate immunity as the first line of species-specific defence

Innate immunity represents the immediate defence system against invading pathogens and includes physical barriers, pattern-recognition receptors (PRRs), complement, macrophages, neutrophils, dendritic cells, natural killer (NK) cells, interferons and inflammatory mediators. Recognition of pathogen-associated molecular patterns (PAMPs) by receptors such as Toll-like receptors, RIG-I-like receptors, NOD-like receptors and cytosolic DNA sensors initiates signalling cascades that activate transcription factors and induce cytokines, chemokines and antimicrobial mechanisms [13].

The outcome of innate immune activation, however, is not uniform across mammals. Differences in receptor expression, signalling thresholds, cytokine production and cellular responses can substantially alter the balance between pathogen elimination and immunopathology. The thesis highlights that excessive inflammatory activation may produce tissue injury and systemic complications, demonstrating that the same immune machinery responsible for protection can also contribute to mortality when inadequately regulated. Recent comparative studies reinforce this concept by demonstrating measurable differences in innate responses between closely related large-animal species exposed to the same bacterial pathogen. For example, comparative investigation of bison and cattle responses to *Mannheimia haemolytica* identified species-associated differences in innate immune responses, illustrating how host background can influence the biological consequences of infection [14].

An important emerging concept is trained innate immunity, whereby innate immune cells can acquire a form of functional memory following previous stimulation. This phenomenon may alter subsequent responses to infection or vaccination and is increasingly being investigated in farm animals. Recent literature indicates that trained immunity could become relevant to veterinary disease prevention and may provide alternatives or complements to conventional antimicrobial approaches. Such findings broaden the traditional concept of innate immunity from a simple, non-specific first-line defence toward a highly plastic system capable of adaptation [15].

Adaptive immunity and immunological memory

Adaptive immunity provides antigen-specific protection through B and T lymphocytes. B cells undergo activation, clonal expansion, antibody production, affinity maturation and immunological memory, whereas T lymphocytes contribute through helper, regulatory and cytotoxic functions. Antibodies can neutralize pathogens and toxins, promote opsonization and activate complement, while T cells provide cellular control of infected or transformed cells. The thesis describes these processes as fundamental components of host defence and emphasizes their importance in controlling infection and generating long-term immunological memory [16].

Although the fundamental principles of adaptive immunity are conserved, the molecular organization and functional characteristics of adaptive immune systems differ considerably among mammalian species. Differences in major histocompatibility complex (MHC) diversity, immunoglobulin repertoires,

lymphocyte populations and immune-regulatory pathways may affect susceptibility to pathogens and the effectiveness of vaccination. Modern comparative research is increasingly overcoming a historical limitation in veterinary immunology: the lack of species-specific reagents for characterizing immune-cell populations. Advances in monoclonal antibodies against MHC and leukocyte differentiation molecules have expanded the ability to study immune evolution and function in horses, cattle, bison, buffalo, sheep, goats, pigs and camelids [17].

This is particularly important for vaccine development. Protective immunity cannot necessarily be defined using identical immunological correlates across species. Current research in livestock viral diseases emphasizes the need to integrate innate, humoral and cellular immune characteristics when identifying correlates of protection. Consequently, comparative immunology may facilitate the design of vaccines that are tailored to species-specific immune architectures rather than relying exclusively on principles derived from murine or human systems.

Immune resistance versus disease tolerance

One of the most important conceptual distinctions emerging from comparative immunology is the difference between resistance and tolerance. Resistance refers to the capacity of a host to reduce pathogen burden, whereas tolerance refers to the capacity to limit pathological damage caused by infection without necessarily eliminating the pathogen completely.

The thesis provides several examples of this phenomenon, particularly in bats, which may carry viruses with limited clinical manifestations. This observation challenges the conventional assumption that successful immunity necessarily requires complete pathogen elimination. Instead, disease outcome may depend on the ability of the host to establish an equilibrium between pathogen replication and tissue protection.

This distinction has substantial therapeutic implications. A pathogen-directed strategy attempts to eliminate or suppress the infectious agent, whereas a tolerance-oriented strategy may aim to preserve host tissues by controlling excessive inflammation, oxidative stress, vascular injury or pathological cell death. Such host-directed approaches could theoretically remain effective even when pathogens develop resistance to conventional antimicrobial or antiviral therapies.

The concept is also relevant to livestock diseases. Naturally occurring differences between susceptible and tolerant breeds can provide valuable experimental systems for identifying molecular pathways associated with disease tolerance. In bovine trypanosomosis, for example, tolerant and susceptible cattle have been studied to understand differences in innate and adaptive immune responses, immune suppression and mechanisms underlying tolerance to infection [17].

Inflammation: the protective response that can become lethal

Inflammation is essential for pathogen containment and tissue repair, but uncontrolled inflammation can become a major driver of disease severity. Following pathogen recognition, macrophages, neutrophils and dendritic cells release cytokines and chemokines that recruit additional immune cells and amplify antimicrobial responses. If this response becomes excessive or persists after the pathogen has been controlled, inflammatory mediators can damage endothelial cells, epithelial barriers and parenchymal tissues.

The thesis identifies excessive inflammatory activation as an important mechanism connecting immune defence with tissue damage and mortality. It further highlights cytokine signalling, apoptosis, necroptosis and mitochondrial pathways as important determinants of lethal disease progression.

This concept is particularly relevant to severe viral infections, where pathogen-induced damage may be compounded by dysregulated host responses. Comparative species studies can therefore identify hosts that have evolved mechanisms for maintaining antiviral activity while limiting inflammatory pathology [18].

Species-specific immune adaptation: an evolutionary perspective

Large mammals have experienced different evolutionary pressures arising from body size, lifespan, metabolic rate, ecological environment, diet, pathogen exposure and reproductive strategy. These pressures have shaped immune systems that are not simply larger versions of the immune systems of small mammals. Instead, different species have developed specialized solutions to their particular biological challenges.

For example, a large and long-lived animal must maintain genomic and cellular integrity over an extended lifetime while simultaneously controlling infection and avoiding excessive inflammation. In contrast, species exposed to high pathogen diversity may benefit from expanded or specialized antibody repertoires. Comparative analysis of these adaptations therefore provides an opportunity to identify biological

mechanisms that have already been optimized by evolution.

The thesis highlights three particularly important examples: enhanced tumour suppression in elephants, heavy-chain-only antibodies in camelids and antiviral tolerance in bats. These examples provide a useful conceptual framework for the remainder of this review because they represent three complementary forms of biological innovation: genomic protection, molecular recognition and controlled antiviral immunity.

Camelids: an evolutionary innovation in antibody architecture

Camelids provide one of the clearest examples of species-specific innovation in adaptive immunity. In addition to conventional antibodies, camelids produce heavy-chain-only antibodies (HCAbs). Their variable antigen-binding domains, termed VHHs or nanobodies, are exceptionally small compared with conventional antibodies while retaining antigen-recognition capability.

The thesis identifies camelid heavy-chain antibodies as an important species-specific adaptation and highlights their potential for therapeutic development. Recent research published in 2026 provides an updated understanding of camelid innate and adaptive immunity and emphasizes the distinctive nature of heavy-chain-only antibodies, somatic hypermutation and camelid T-cell populations. The same review highlights nanobody-based diagnostics and therapeutics as major biomedical applications.

Nanobodies are approximately 15 kDa and possess a compact structure that can provide advantages including high stability, solubility, tissue penetration and accessibility to antigenic sites that may be difficult for conventional antibodies to reach. Their relatively small size also makes them attractive candidates for molecular imaging, biosensing, targeted therapy and intracellular applications. Modern nanobody research has expanded further toward AI-assisted structure prediction, rational engineering and immunogenicity assessment.

Thus, camelid immunity demonstrates how a naturally occurring immune adaptation can be transformed into a pharmaceutical technology. This represents a central theme of comparative immunology: evolutionary diversity can function as a reservoir of therapeutic innovation [19].

Large-animal immunity as a translational research platform

The significance of comparative immunology extends beyond veterinary medicine. Large animals can reproduce anatomical, physiological and immunological characteristics that may be difficult to model in mice.

Their larger body size can facilitate longitudinal sampling, repeated tissue assessment and evaluation of pharmacological interventions. Furthermore, several large species develop naturally occurring diseases that share clinically relevant characteristics with human disorders.

Recent evidence emphasizes that large-animal research contributes to understanding infectious disease transmission, antibody responses, vaccination, transplantation and immunotherapy. Consequently, large mammals should be considered complementary rather than competing models within biomedical research.

A particularly promising strategy is to combine comparative immunology, genomics, transcriptomics, proteomics and systems biology to identify conserved protective pathways and species-specific adaptations. Such integration could reveal molecular signatures associated with resistance, tolerance or susceptibility and may ultimately support precision veterinary medicine and human therapeutics [15].

Species-Specific Immunological Adaptations as Natural Models of Disease Resistance

The remarkable diversity of mammalian immune systems suggests that susceptibility to lethal disease is not simply a fixed property of a pathogen. Instead, it is an emergent property of the interaction between pathogen biology and host-specific immune architecture. The thesis emphasizes that species variation can influence immune efficiency, inflammatory responses and pathogen tolerance [13].

These adaptations should not be considered isolated curiosities. Together, they demonstrate a broader principle: evolution has generated multiple solutions to the biological problem of surviving persistent environmental and infectious stress.

Recent research in camelids, for example, demonstrates that adaptation occurs across both innate and adaptive immune compartments rather than being restricted to antibody structure. Similarly, research on large-animal immunology increasingly recognizes that comparative studies can reveal immune mechanisms that are poorly represented in conventional mouse models.

Table 1: Model, Principal adaptation, biological significance and translational relevance.

Species/model	Principal adaptation	Biological significance	Translational relevance
Elephants	Expanded TP53-associated tumour-suppression mechanisms	Enhanced surveillance of potentially malignant cells	Cancer prevention and genomic stability
Camelids	Heavy-chain-only antibodies/VHHs	Compact and highly versatile antigen recognition	Nanobody-based drugs, diagnostics and imaging
Bats	Strong antiviral readiness with controlled inflammation	Viral tolerance with reduced immunopathology	Host-directed antiviral therapy
Disease-tolerant livestock	Breed/species-specific immune regulation	Reduced pathology despite infection	Disease-resistant breeding and immunomodulation
Large-animal biomedical models	Human-relevant physiology and immunity	Improved translational modelling	Vaccines, immunotherapy and drug development

Therefore, the next generation of comparative immunology should move from merely describing species differences toward identifying mechanism–phenotype–translation relationships. In this framework, a naturally occurring phenotype such as viral tolerance, cancer resistance or pathogen tolerance becomes the starting point for identifying molecular pathways, validating them experimentally and ultimately developing interventions for other species, including humans.

Species-Specific Immune Adaptations in Large Mammals: Molecular Strategies for Surviving Lethal Disease

The comparison of immune responses across mammalian species demonstrates that survival from severe disease is determined not simply by the ability to recognize and eliminate a pathogen, but also by the capacity to regulate inflammation, preserve tissue integrity and maintain physiological homeostasis. The thesis identifies this interaction between pathogen characteristics, host immunity, cellular defence mechanisms and environmental influences as a major determinant of disease progression and survival. Recent comparative immunology research similarly emphasizes that large and agricultural animals can reveal immune mechanisms that are not adequately represented in conventional laboratory rodents, particularly in infectious diseases, antibody responses, vaccination and immunotherapy [20].

A useful way to understand this phenomenon is to consider large mammals as naturally evolved immunological experiments. Each species has experienced different combinations of pathogen exposure, body size, longevity, metabolism, ecological pressures and reproductive strategies. Consequently, evolution has produced different solutions to common biological challenges. Some species primarily enhance pathogen recognition and clearance, whereas others have developed sophisticated mechanisms for controlling inflammation and tissue damage. Still others have evolved unusual antibody structures or enhanced mechanisms of genomic surveillance.

The thesis particularly identifies elephants, camelids and bats as important examples of such adaptations, with enhanced tumour suppression, heavy-chain-only antibodies and viral tolerance respectively. These examples can be viewed as three complementary biological strategies: protecting the genome, improving molecular recognition and controlling immunopathology.

Elephants: balancing longevity, body size and cancer protection

Large body size and prolonged lifespan theoretically increase the number of cells and the duration over which somatic mutations can accumulate. Nevertheless, large and long-lived mammals such as elephants do not exhibit cancer rates that simply scale with the number of cells or years lived. This apparent contradiction is commonly discussed within the framework of Peto's paradox, which has stimulated considerable interest in naturally evolved cancer-protection mechanisms.

The elephant therefore provides a valuable comparative model for investigating how large mammals maintain genomic integrity while avoiding malignant transformation. The thesis specifically identifies enhanced tumour suppression through the TP53 system

as one of the distinctive adaptations of elephants. The broader literature supports the importance of TP53-related mechanisms in elephant cancer biology, although cancer resistance in elephants should not be attributed exclusively to TP53; it is likely to involve multiple interacting genomic, cellular and physiological mechanisms [21].

The central function of p53 is to respond to cellular stress, particularly DNA damage, oncogenic signalling and other conditions threatening genomic stability. Activation of p53 can promote cell-cycle arrest, DNA repair, senescence or apoptosis depending on cellular context. Consequently, enhanced p53-mediated surveillance can theoretically eliminate potentially malignant cells before they progress into clinically significant tumours.

This provides an important conceptual connection between immunity and cancer biology. Although TP53 is not conventionally categorized as an immune molecule, its function intersects with immune surveillance, inflammatory signalling and programmed cell death. The ability to recognize and eliminate damaged cells therefore represents a broader form of biological defence in which genomic integrity and immune homeostasis are interconnected.

Translational significance

The elephant model may provide useful insights into:

- mechanisms of DNA-damage sensing;
- regulation of apoptosis;
- tumour-suppressor pathway activation;
- genomic stability;
- cellular stress responses;
- mechanisms underlying Peto's paradox; and
- potential strategies for cancer prevention.

Importantly, comparative oncology should focus not merely on identifying a single "cancer resistance gene" but on reconstructing the network of molecular adaptations that permits large mammals to maintain tissue integrity over long lifespans.

Camelids: heavy-chain-only antibodies as an evolutionary platform for precision medicine

Camelids—including camels, llamas and alpacas—represent another striking example of immune-system innovation. In addition to conventional immunoglobulins, camelids produce heavy-chain-only antibodies (HCAbs). Their antigen-binding component can function as a single variable heavy-chain domain, commonly referred to as VHH or nanobody [22].

The thesis identifies heavy-chain-only antibodies as a distinctive camelid adaptation and emphasizes their biomedical potential. This observation has become particularly important because nanobodies have progressed from an unusual biological phenomenon to a clinically relevant antibody-engineering platform.

Conventional immunoglobulin G contains paired heavy and light chains. In contrast, camelid VHH domains function independently without requiring a light-chain partner. This compact structure provides several advantages, including relatively low molecular weight, high stability and the capacity to recognize epitopes that may be poorly accessible to conventional antibodies. Contemporary reviews describe these properties as important reasons for the expanding application of nanobodies in research, diagnostics and therapy.

The small size of VHH molecules is particularly important. Conventional antibodies may encounter steric limitations when binding recessed or cryptic antigenic sites. Nanobodies, because of their compact structure and elongated complementarity-determining region 3 (CDR3), can access some of these otherwise difficult epitopes.

The resulting biological platform has applications extending across:

1. infectious disease diagnostics;
2. viral neutralization;
3. cancer targeting;
4. molecular imaging;
5. drug delivery;
6. bispecific and multispecific therapeutics;
7. targeted protein degradation;
8. biosensor development; and
9. intracellular protein targeting.

Recent literature indicates that nanobodies are increasingly being incorporated into complex therapeutic architectures rather than being used solely as simple antigen-binding fragments. As of 2025, multiple VHH-containing therapeutics had received marketing authorization, demonstrating that camelid-inspired antibody engineering has progressed into clinical medicine.

Nanobody engineering and the transition from natural immunity to therapeutic design

The biomedical importance of camelid antibodies lies not only in their natural structure but also in their engineerability. VHH domains can be reformatted into multivalent, bispecific or multispecific molecules, fused with Fc domains, linked to albumin-binding domains,

conjugated to imaging agents or incorporated into engineered cellular therapies [23].

This represents a particularly important example of how comparative immunology can contribute directly to pharmaceutical innovation:

Natural evolutionary adaptation → molecular characterization → recombinant production → engineering → preclinical validation → clinical translation

Such a pathway transforms an unusual species-specific immune feature into a general biomedical technology.

Nanobodies are also being investigated for cancer therapy because their small size and tissue penetration may offer advantages for tumour targeting. Nevertheless, rapid renal clearance and challenges associated with prolonged systemic exposure remain important limitations.

Therefore, the camelid model illustrates both the opportunities and limitations of translating evolutionary adaptations into therapeutics.

Bats: a model of viral tolerance rather than simple viral resistance

Among mammalian species, bats have attracted exceptional attention because they can serve as reservoirs for numerous viruses while often exhibiting limited clinical disease. The thesis devotes a substantial section to comparing SARS-CoV-2 infection in humans and bats and emphasizes differences in interferon responses, oxidative stress, DNA repair and adaptive immune regulation.

The significance of bats lies in the apparent ability of some species to maintain a functional equilibrium between viral replication and host health. Rather than producing an excessively aggressive inflammatory response, bats can control infection while limiting the tissue injury associated with immune activation.

Recent research specifically identifies regulation of inflammation and programmed cell death as important components of bat viral tolerance.

In particular, pathways involving pyroptosis and necroptosis are increasingly being investigated because excessive activation of inflammatory cell death contributes to tissue injury during severe viral disease in humans [24].

Interferon responses and antiviral preparedness

Interferons are among the most important components of antiviral innate immunity. Recognition of viral nucleic acids activates interferon signaling and induces interferon-stimulated genes (ISGs), which establish an intracellular antiviral state.

The thesis describes bats as capable of mounting rapid antiviral responses while limiting excessive inflammatory signalling. Such a combination is potentially advantageous because delayed antiviral signalling may permit extensive viral replication, whereas excessive late inflammatory activation can produce substantial tissue damage.

The biological importance of bats therefore appears to involve not simply stronger immunity, but rather better regulation of immunity.

This distinction is crucial. An immune response that is excessively weak may allow uncontrolled pathogen replication, whereas an excessively strong response may cause immunopathology. Disease tolerance emerges when these competing pressures are appropriately balanced [25].

Oxidative stress, metabolism and cellular protection in bats

Viral infection can generate oxidative stress through mitochondrial dysfunction, inflammatory signalling and altered cellular metabolism. Excessive reactive oxygen species (ROS) can damage proteins, membranes and DNA.

The thesis describes bats as possessing adaptations associated with high metabolic activity, enhanced DNA repair and antioxidant defence. These mechanisms are particularly interesting because bats have exceptionally high metabolic demands during flight.

The relationship between metabolism and immunity may therefore be an important component of disease tolerance. Instead of viewing immune responses independently of cellular metabolism, future comparative studies should investigate the immunometabolic architecture that permits certain species to maintain tissue homeostasis under conditions that would otherwise generate severe oxidative and inflammatory injury [26].

Potential mechanisms of interest include:

- mitochondrial quality control;
- antioxidant systems;
- DNA damage repair;
- cellular stress responses;
- metabolic reprogramming;
- inflammatory signalling;
- autophagy; and
- regulation of programmed cell death.

The integration of these pathways may explain why some bat species can tolerate viral infection with comparatively limited tissue pathology.

Regulation of programmed cell death: a critical determinant of disease outcome

Programmed cell death is essential for maintaining tissue homeostasis and eliminating damaged or infected cells. However, during severe infection, excessive activation of cell-death pathways can contribute directly to tissue destruction.

The thesis identifies apoptosis, necroptosis and other regulated cell-death mechanisms as important contributors to disease severity. Recent bat research expands this concept by emphasizing pyroptosis and necroptosis as potential mechanisms underlying differences in inflammatory pathology between bats and humans.

This suggests that future therapeutic strategies should potentially target not only pathogen replication but also the host cell-death response.

For example:

Viral infection → pathogen recognition → inflammatory signalling → cell-death activation → tissue damage

may become:

Viral infection → controlled antiviral signalling → restricted inflammatory cell death → preservation of tissue integrity → improved survival

The second pathway represents the biological principle of disease tolerance.

Large mammals as reservoirs of immunological innovation

The examples of elephants, camelids and bats demonstrate that species-specific adaptations can occur at multiple biological levels.

Table 2: List of biological level, representative species, major adaptation and potential biomedical lessons.

Biological level	Representative species	Major adaptation	Potential biomedical lesson
Genomic	Elephant	TP53-associated tumour surveillance	Cancer prevention and genomic stability
Humoral	Camelid	Heavy-chain-only antibodies	Nanobody therapeutics and diagnostics
Innate antiviral	Bat	Rapid/regulated antiviral responses	Host-directed antiviral therapy
Inflammatory regulation	Bat	Controlled inflammatory cell death	Reduction of immunopathology
Cellular stress	Bat	Oxidative stress and DNA-repair adaptations	Cytoprotection
Comparative disease tolerance	Livestock	Breed/species-dependent immune phenotypes	Disease-resistant breeding and immunomodulation
Translational modelling	Large animals	Physiological and immunological relevance	Vaccines and therapeutic development

The importance of this framework is that these mechanisms should not be studied independently. Genomic surveillance, antibody recognition, interferon responses, inflammation, oxidative stress and programmed cell death form interconnected biological networks.

A pathogen may therefore exploit one pathway while the host compensates through another. For example, suppression of interferon signaling may be counterbalanced by alternative innate mechanisms; persistent viral replication may be tolerated through improved control of inflammatory damage; and cellular damage may be limited through enhanced DNA repair or antioxidant mechanisms [19].

Pathogen immune evasion versus host immune adaptation

The thesis identifies several mechanisms through which pathogens may overcome host defence, including suppression of interferon signalling, reduction of antigen presentation, induction of apoptosis and chronic immune activation. These mechanisms illustrate that

disease progression is the outcome of an evolutionary contest between pathogen strategies and host counterstrategies.

Pathogens have evolved mechanisms to:

- avoid innate immune recognition;
- suppress interferon signalling;
- interfere with antigen presentation;
- manipulate apoptosis;
- alter cytokine networks;
- establish persistent infection;
- induce immune exhaustion; and
- exploit host-cell machinery for replication.

Hosts, in contrast, have evolved mechanisms to detect infection, restrict pathogen replication, eliminate infected cells and repair damaged tissues.

The resulting interaction can be represented as:

Pathogen virulence + immune evasion
↓
Host recognition + immune resistance
↓
Inflammatory regulation + cellular protection
↓
Disease resistance or disease tolerance
↓
Recovery, persistence or mortality

This framework is particularly useful for explaining why pathogen virulence alone cannot predict clinical outcome.

From comparative immunology to host-directed therapeutics

The identification of naturally disease-tolerant species provides a rationale for developing **host-directed therapies (HDTs)**. Conventional antimicrobial treatment primarily targets the pathogen. HDTs instead modify host pathways involved in disease progression.

Potential therapeutic targets emerging from comparative immunology include:

Interferon signalling

Modulation of interferon pathways may improve early antiviral defence while avoiding excessive downstream inflammation.

Cytokine regulation

Selective inhibition of pathological cytokine signalling may reduce tissue injury while preserving antimicrobial immunity.

Inflammasome regulation

Controlled modulation of inflammasome activation may reduce pyroptosis and excessive inflammatory responses.

Cell-death pathways

Selective modulation of apoptosis, necroptosis or pyroptosis could potentially reduce tissue destruction during severe infection.

Oxidative stress

Enhancement of endogenous antioxidant and mitochondrial-protective mechanisms may improve cellular survival during infection.

Antibody engineering

Camelid-derived VHHs provide a particularly advanced example of converting comparative immunological knowledge into targeted therapeutics. Recent literature demonstrates applications in multispecific antibodies, molecular imaging, drug delivery and engineered cellular therapies [23].

The emerging concept of an evolutionary medicine framework

The combined evidence from elephants, camelids, bats and other large mammals supports a broader evolutionary medicine framework in which naturally occurring species adaptations are treated as sources of therapeutic hypotheses.

Integrative model: from natural adaptation to therapeutic discovery

The central concept emerging from this review can be summarized as follows:

Evolutionary pressure
↓
Species-specific adaptation
↓
Molecular/cellular mechanism
↓
Disease resistance or tolerance
↓
Mechanistic validation
↓
Therapeutic target/platform
↓
Drug, vaccine, antibody or host-directed intervention

For elephants, this pathway begins with the evolutionary challenge of maintaining genomic stability despite large body size and longevity. For camelids, it involves an unusual antibody architecture that has evolved into the nanobody platform. For bats, it involves the ability to coexist with potentially pathogenic viruses while limiting inflammatory and cellular damage.

These examples collectively support the central hypothesis of this review: large mammals constitute an evolutionary library of naturally optimized solutions to disease, and comparative immunology provides the framework for decoding these solutions for translational medicine [21].

Molecular and Cellular Mechanisms of Lethal Disease in Large Mammals

Lethal disease in large mammals is rarely attributable to a single pathological event. Instead, mortality generally results from a progressive interaction among pathogen replication, immune recognition, inflammatory signalling, cellular injury, vascular dysfunction, metabolic disturbance and failure of essential organs. The thesis specifically describes lethal diseases in cattle, horses and sheep as conditions that may involve rapid microbial or viral dissemination, septicemia, toxin release, organ-system failure and metabolic collapse, with death occurring within hours or days in severe cases [27].

A major conclusion emerging from the thesis is that the pathogen itself is only one component of disease severity. Host immune dysregulation can amplify the original pathological stimulus and transform a localized infection into systemic disease. The discussion chapter identifies immune evasion, suppression of immune signalling, excessive inflammatory responses, immune exhaustion and tissue damage as interconnected processes contributing to mortality. Recent experimental and clinical research similarly demonstrates that severe disease may result from the combined effects of pathogen-mediated damage and dysregulated host responses. For example, virulent African swine fever virus (ASFV) infection is associated with marked cytokine dysregulation, lymphoid depletion, vascular injury and systemic inflammation.

This section therefore considers lethal disease as a multistage biological cascade, beginning with pathogen entry and recognition and progressing through inflammatory amplification, cellular dysfunction, immune failure and ultimately organ-system collapse [28].

Pathogen Entry, Recognition and Initial Host Response

The first stage of infectious disease is the interaction between the pathogen and host tissues. Pathogens must overcome physical barriers, attach to susceptible cells, enter the host and exploit cellular machinery for replication. The host simultaneously attempts to identify the invading organism through innate immune surveillance.

Pattern-recognition receptors (PRRs) recognize conserved pathogen-associated molecular patterns (PAMPs), including microbial nucleic acids, lipopolysaccharide, proteins and other pathogen-derived structures. Damage-associated molecular patterns (DAMPs) released from injured host cells can further amplify the response.

The thesis identifies PRRs, PAMP recognition, macrophages, neutrophils, dendritic cells and inflammatory signalling as central components of the initial innate response [29].

The initial response can therefore be represented as:

Pathogen entry → PAMP recognition → PRR activation → cytokine/interferon production → cellular recruitment → pathogen restriction

Under normal circumstances, this process remains sufficiently controlled to eliminate or contain the pathogen while limiting host tissue damage. In lethal disease, however, this equilibrium may be disrupted.

Pattern-Recognition Receptors and Innate Immune Signalling

PRRs function as molecular surveillance systems. Important families include Toll-like receptors (TLRs), RIG-I-like receptors, NOD-like receptors and cytosolic DNA-sensing pathways.

Activation of these receptors can stimulate signalling pathways involving:

- NF-κB;
- interferon regulatory factors (IRFs);
- JAK–STAT signalling;
- inflammasomes;
- type I interferons;
- pro-inflammatory cytokines; and
- chemokines.

The resulting signals coordinate the recruitment and activation of macrophages, neutrophils, dendritic cells and NK cells.

However, pathogens have evolved mechanisms to interfere with these pathways. The thesis specifically identifies suppression of interferon signalling and reduction of antigen presentation as important immune-evasion mechanisms.

African swine fever provides a particularly informative example. ASFV can interfere with cGAS–STING signalling, cytokine production, NF-κB-associated inflammatory pathways and other components of innate antiviral immunity [30].

Thus, the outcome of infection depends partly on the competition between:

host pathogen sensing and pathogen-mediated immune suppression.

Interferon Signalling and Antiviral Defence

Interferons constitute a major component of innate antiviral immunity. Following recognition of viral nucleic acids, infected and neighbouring cells can produce interferons that activate interferon-stimulated genes (ISGs). These genes establish an intracellular antiviral state and restrict multiple stages of viral replication.

The thesis emphasizes the importance of interferon responses in both disease progression and species-specific viral tolerance. In bats, rapid and regulated interferon activity is proposed as one component of their ability to control viral infection without excessive inflammatory damage.

In contrast, pathogens capable of suppressing interferon signalling may gain a critical advantage during the early phase of infection. ASFV, for example, has evolved multiple mechanisms that interfere with interferon production and downstream antiviral signalling.

This creates an important temporal relationship:

Early interferon response → rapid pathogen restriction

whereas:

Delayed/suppressed interferon response → increased pathogen replication → greater antigen burden → stronger subsequent inflammation

This distinction may help explain why immune responses that appear quantitatively strong during later stages of disease may nevertheless fail to provide protection.

Cytokine Dysregulation and the Cytokine-Storm Phenomenon

Cytokines are essential signalling molecules that coordinate innate and adaptive immunity. Controlled cytokine production promotes pathogen elimination, recruitment of immune cells and tissue repair. However, excessive and sustained cytokine production can produce systemic inflammation and contribute directly to tissue injury.

The thesis identifies cytokine storms as a potentially important mechanism in severe infectious diseases and emphasizes the relationship between excessive inflammatory responses, tissue damage and mortality.

ASFV provides a well-characterized example. Virulent infection has been associated with increased concentrations of IL-1α, IL-1β, IL-6, TNF and several chemokines. These mediators are associated with lymphoid depletion, hemorrhage and edema [31].

The pathophysiological sequence can be conceptualized as:

Pathogen replication
↓
Macrophage and innate-cell activation
↓
IL-1β, IL-6, TNF-α and chemokine release
↓
Leukocyte recruitment + endothelial activation
↓
Vascular permeability + tissue inflammation
↓
Edema, hemorrhage and tissue hypoxia
↓
Organ dysfunction
↓
Mortality

Importantly, the term "cytokine storm" should not be interpreted simply as an increase in every cytokine. The biological outcome depends on the magnitude, timing, location and balance between pro-inflammatory and regulatory mediators.

Macrophages as Central Regulators of Disease Progression

Macrophages occupy a particularly important position at the interface between pathogen replication and host inflammation. They can recognize pathogens, produce inflammatory mediators, phagocytose microorganisms

and damaged cells, present antigens and influence adaptive immune responses.

However, some pathogens exploit macrophages as sites of replication or manipulate their signalling functions. ASFV is a prominent example: monocytes and macrophages are major cellular targets for viral replication. Infection can therefore simultaneously promote viral propagation and inflammatory signalling [32].

Lymphoid Depletion and Immune Collapse

Severe infectious disease may paradoxically produce both hyperinflammation and immunosuppression. These phenomena are not mutually exclusive.

The thesis identifies immune exhaustion, cellular dysfunction and reduced immune efficiency as important consequences of prolonged or severe infection.

ASFV provides a particularly clear example. Although the infection stimulates intense inflammatory responses, it can simultaneously produce extensive lymphocyte apoptosis and lymphoid depletion.

Consequently, the host may enter a state characterized by:

- excessive innate inflammation;
- reduced adaptive immune competence;
- lymphocyte depletion;
- impaired antigen-specific responses;
- increased susceptibility to secondary complications; and
- progressive systemic dysfunction.

This apparent contradiction is highly relevant to lethal disease because hyperactivation of one immune compartment can coexist with functional suppression of another.

Antigen Presentation and Adaptive Immune Failure

Effective adaptive immunity requires antigen processing and presentation through major histocompatibility complex (MHC) molecules. Antigen-presenting cells, particularly dendritic cells and macrophages, communicate pathogen-derived information to T lymphocytes [33].

Interference with antigen presentation can therefore delay or weaken adaptive immunity.

The thesis identifies reduction in antigen presentation as one of the mechanisms through which pathogens can evade host immunity.

Pathogen-mediated disruption of antigen presentation may result in:

Reduced antigen recognition → impaired T-cell activation → delayed pathogen clearance → persistent antigen exposure → prolonged inflammation.

This mechanism is particularly important for pathogens with sophisticated immune-evasion strategies.

Apoptosis and Regulated Cell Death in Lethal Disease

Programmed cell death is fundamental to tissue homeostasis. Apoptosis allows the controlled removal of damaged, infected or unwanted cells with comparatively limited inflammatory release.

During infection, however, pathogens can manipulate apoptosis to their advantage.

The thesis identifies apoptosis, necroptosis and other regulated cell-death processes as important determinants of disease severity.

ASFV demonstrates the complexity of this process. The virus can inhibit apoptosis in infected cells during early stages, supporting viral replication, while extensive apoptosis of uninfected lymphocytes may subsequently contribute to immune collapse.

Necroptosis, Pyroptosis and Inflammatory Cell Death

Unlike classical apoptosis, several regulated forms of cell death can produce substantial inflammatory signalling.

Pyroptosis is associated with inflammasome activation and inflammatory cytokine release, while necroptosis represents a regulated necrotic pathway capable of releasing intracellular danger signals.

These pathways may provide an effective mechanism for eliminating infected cells but can become pathological when activated excessively.

This issue is particularly relevant to comparative immunology because the thesis describes bats as having adaptations that may limit excessive inflammatory responses and cell damage [34].

The ability to control inflammatory cell death may therefore represent an important component of disease tolerance.

A potentially important evolutionary contrast is:

Susceptible host

Pathogen → excessive inflammasome activation → inflammatory cell death → cytokine amplification → tissue injury

Disease-tolerant host

Pathogen → antiviral recognition → controlled inflammatory signalling → limited cell death → tissue preservation

Oxidative Stress and Mitochondrial Dysfunction

Infection, inflammation and cellular stress can increase production of reactive oxygen species (ROS). At controlled concentrations, ROS participate in antimicrobial defence and cellular signalling. Excessive ROS, however, can damage DNA, proteins, lipids and mitochondrial membranes.

The thesis specifically associates mitochondrial pathways and cellular stress with lethal disease mechanisms. It also highlights enhanced antioxidant capacity and DNA-repair mechanisms as potential contributors to bat viral tolerance.

Mitochondria are particularly important because they are simultaneously:

- energy-producing organelles;
- regulators of oxidative stress;
- contributors to apoptosis;
- components of innate immune signalling; and
- sensors of cellular damage.

Mitochondrial dysfunction can therefore create a pathological feedback loop:

Infection → inflammation → mitochondrial dysfunction → ROS accumulation → cellular injury → DAMP release → further inflammation.

Breaking this cycle could represent an important host-directed therapeutic strategy.

Vascular Injury, Tissue Hypoxia and Organ Failure

As inflammatory disease becomes systemic, endothelial dysfunction can produce increased vascular permeability, edema, hemorrhage and impaired tissue perfusion.

ASFV provides a particularly important example because severe disease involves vascular injury, hemorrhage and systemic inflammatory responses. Recent literature describes cytokine-mediated endothelial dysfunction as a major contributor to vascular permeability and multiorgan dysfunction [35].

The progression can be summarized as:

Inflammatory mediator release
↓
Endothelial activation/injury
↓
Loss of vascular barrier integrity
↓
Fluid leakage and edema
↓
Reduced effective circulating volume
↓
Tissue hypoxia
↓
Organ dysfunction
↓
Multiorgan failure

This mechanism demonstrates why severe infectious disease can become fatal even when pathogen replication is not occurring equally in every organ.

Metabolic Collapse and Systemic Homeostasis

Severe infection imposes substantial metabolic demands on the host. Immune cells require increased energy for proliferation, migration, cytokine production and antimicrobial activity. Simultaneously, fever, tissue injury, altered mitochondrial function and reduced organ perfusion can disturb normal metabolism.

Large mammals may be particularly informative in this context because body size, metabolic rate and lifespan influence physiological responses to infection. The thesis emphasizes that species-specific physiology and metabolism contribute to differences in disease susceptibility and survival [36].

Metabolic disturbances may therefore amplify existing immune pathology by affecting:

- ATP availability;
- mitochondrial function;
- glucose metabolism;
- lipid metabolism;
- oxidative balance;
- electrolyte homeostasis; and
- organ-specific energy requirements.

The final stages of lethal disease can thus be regarded as a transition from localized host–pathogen conflict to systemic loss of physiological homeostasis.

Why Some Pathogens Produce Rapid Mortality

The thesis describes severe lethal disease in large animals as potentially progressing rapidly through

septicemia, viral dissemination, toxin release, organ failure and metabolic collapse.

Rapid mortality is particularly likely when multiple pathological mechanisms occur simultaneously.

Table 3: Pathological events, immediate consequences and systemic consequences.

Pathological events	Immediate consequences	Systemic consequence
Rapid pathogen replication	Increased pathogen burden	Disseminated infection
Immune evasion	Delayed clearance	Persistent replication
Cytokine dysregulation	Excessive inflammation	Tissue injury
Lymphocyte depletion	Adaptive immune failure	Immunosuppression
Endothelial dysfunction	Vascular leakage	Hypotension/hemorrhage
Oxidative stress	Cellular injury	Organ dysfunction
Regulated cell death	Loss of functional cells	Tissue destruction
Metabolic dysfunction	Reduced cellular energy	Physiological collapse
Multiorgan injury	Loss of organ function	Mortality

The critical insight is that these events are interdependent rather than sequential in isolation.

Disease-Specific Examples from the Thesis

The thesis discusses several important large-animal diseases, including bovine leukemia virus (BLV), African swine fever virus (ASFV), bovine respiratory disease (BRD), chronic wasting disease (CWD) and foot-and-mouth disease (FMD). It emphasizes that these diseases demonstrate different combinations of immune evasion, immune suppression, inflammatory dysregulation and tissue damage [32].

Bovine leukemia virus

BLV provides an example of persistent viral infection in which interactions between the virus and host immune system determine long-term disease outcome. Persistent infection can alter lymphocyte biology and immune regulation.

African swine fever

ASFV represents a particularly severe example of immune dysregulation, characterized by macrophage infection, inflammatory cytokine production, lymphocyte apoptosis, vascular damage and systemic disease.

Bovine respiratory disease

BRD illustrates the importance of interactions among infectious agents, host immunity and inflammatory injury within the respiratory tract. Disease severity can depend on both pathogen burden and the host inflammatory response.

Chronic wasting disease

CWD demonstrates a different pathological paradigm in which persistent protein misfolding and neurodegeneration ultimately produce progressive neurological dysfunction.

Foot-and-mouth disease

FMD demonstrates how rapidly transmissible viral infection can interact with host immunity and tissue tropism to produce major disease and substantial agricultural consequences.

These examples reinforce the central argument of the thesis: there is no single mechanism of lethal disease; rather, mortality emerges from disease-specific combinations of pathogen biology and host response [33].

An Integrated Pathophysiological Model of Lethal Disease

Based on the mechanisms identified in the thesis, a unified model can be proposed:

Phase I — Pathogen Entry

Exposure → attachment → cellular entry → replication

↓

Phase II — Host Recognition

PAMP/DAMP recognition → PRR activation → interferon/cytokine signalling

↓

Phase III — Pathogen–Host Conflict

Antiviral immunity ↔ pathogen immune evasion

↓

Phase IV — Immune Amplification

Macrophage/DC activation → cytokine and chemokine release → leukocyte recruitment

↓

Phase V — Immunopathology

Cytokine dysregulation → inflammasome activation → apoptosis/pyroptosis/necroptosis → tissue injury

↓

Phase VI — Systemic Dysfunction

Endothelial injury → vascular leakage → hypoxia → metabolic disturbance

↓

Phase VII — Organ Failure

Lung/liver/kidney/vascular/immune dysfunction

↓

Final Outcome

Recovery ↔ chronic disease ↔ disease tolerance ↔ mortality

The precise position at which an individual host enters one of these outcomes is influenced by species-specific immune regulation, pathogen virulence, infectious dose, tissue tropism, age, physiological condition and environmental factors.

Comparative Perspective: Why Disease Tolerance Matters

The thesis provides a particularly important contrast between disease progression in humans and viral tolerance in bats. Bats can exhibit rapid antiviral responses while avoiding the excessive inflammation and cellular damage associated with severe disease in susceptible hosts.

This comparison suggests that future therapeutic research should not focus exclusively on eliminating pathogens. It should also investigate mechanisms that allow naturally tolerant species to preserve tissue function during infection.

Translational Opportunities Emerging from Lethal-Disease Mechanisms

Understanding the molecular basis of lethal disease provides several potential therapeutic directions.

Antiviral and antimicrobial therapy

Reducing pathogen replication remains essential, particularly during the early phase of disease.

Host-directed therapy

Modulating host pathways rather than directly targeting pathogens may reduce disease severity while limiting the emergence of pathogen resistance.

Cytokine modulation

Selective modulation of IL-1, IL-6, TNF and related pathways may reduce immunopathology in appropriately selected disease settings.

Inflammasome targeting

Controlled modulation of inflammasome activity may reduce excessive inflammatory cell death.

Antioxidant and mitochondrial protection

Reducing oxidative damage and preserving mitochondrial function may protect tissues during severe infection.

Immune restoration

Strategies aimed at preserving lymphocyte function, antigen presentation and immunological memory may counteract immune exhaustion.

Comparative antibody technology

Camelid-derived VHHs provide a distinct route toward pathogen-specific therapeutics and diagnostics.

Disease-tolerance mimetics

Perhaps the most innovative direction is the development of drugs that mimic naturally evolved disease-tolerance mechanisms observed in bats and other tolerant species.

Comparative Immunological Responses to Major Lethal Diseases in Large Mammals

The preceding sections demonstrate that lethal disease is determined by a dynamic interaction between pathogen virulence, host immune responses, cellular defence mechanisms and species-specific physiological characteristics. The thesis specifically identifies bovine leukemia virus (BLV), African swine fever virus (ASFV), bovine respiratory disease (BRD), chronic wasting disease (CWD) and foot-and-mouth disease (FMD) as important examples in which immune evasion, inflammatory dysregulation, tissue damage and immune exhaustion influence disease progression.

Comparative analysis of these diseases is particularly valuable because each represents a different pathogen–host interaction. Some pathogens establish persistent infection, some produce acute systemic inflammation, some primarily damage the respiratory system, while others induce progressive neurological degeneration. Consequently, there is no universal immunological mechanism of lethality. Instead, disease outcome depends on how individual pathogens interact with the immune architecture of their respective hosts [37].

Recent literature supports the value of large-animal species in this context. Large and agricultural animals can provide information on infectious disease spread, antibody responses, vaccine development and immunotherapy that cannot always be adequately captured by conventional rodent models.

Bovine Leukemia Virus: Persistence, Immune Dysregulation and Lymphoproliferation

Bovine leukemia virus (BLV) represents an important model of persistent viral infection in cattle. Rather than producing immediate acute mortality in every infected animal, BLV can establish long-term infection and alter lymphocyte biology. This makes BLV particularly relevant for understanding the distinction between infection, persistence and clinical disease.

The thesis identifies persistent infection and immune dysregulation as important components of severe disease. The prolonged interaction between virus and host immune system may eventually alter immune-cell function and contribute to disease progression.

From a comparative perspective, BLV illustrates an important principle: pathogen survival within the host can be more important than rapid pathogen-mediated destruction. The virus benefits from avoiding complete immune elimination, while the host attempts to maintain sufficient immune surveillance without producing excessive tissue damage [38].

African Swine Fever: A Model of Acute Immunopathology

African swine fever (ASF) provides one of the clearest examples of a rapidly progressive lethal disease in a large mammal. Virulent ASF virus can infect macrophage-lineage cells and trigger profound systemic pathology involving inflammation, lymphoid depletion, vascular injury and organ dysfunction.

The project identifies ASFV as a disease in which pathogens can evade immune detection, suppress immune signalling and stimulate excessive inflammatory responses.

Experimental and review literature further indicates that ASFV interacts extensively with host innate immune pathways and can interfere with interferon production, inflammatory signalling and cellular survival mechanisms.

The significance of ASF is therefore not limited to swine health. It represents a valuable model for studying how viral immune evasion and host immunopathology can occur simultaneously [39].

Central pathogenic sequence

ASFV infection
↓
Macrophage infection and innate immune activation
↓
Cytokine/chemokine dysregulation
↓
Lymphocyte depletion + vascular injury
↓
Systemic inflammation
↓
Tissue injury and organ dysfunction
↓
Mortality

This model reinforces the conclusion of the thesis that pathogen virulence alone cannot fully explain disease outcome; host inflammatory regulation is also critical.

Bovine Respiratory Disease: Immunity at the Respiratory Interface

Bovine respiratory disease (BRD) illustrates a different type of host–pathogen interaction. The respiratory tract represents a highly specialized immunological interface continuously exposed to environmental microorganisms, particulate matter and airborne pathogens [40].

Disease development may involve interactions among infectious agents, respiratory epithelial barriers, innate immunity, adaptive immunity and environmental stressors.

Chronic Wasting Disease: Immune Silence and Progressive Neurodegeneration

Chronic wasting disease (CWD) represents a fundamentally different pathological paradigm. As a transmissible spongiform encephalopathy, CWD is associated with abnormal prion protein accumulation and progressive neurological degeneration.

The immune response to prions differs substantially from classical antiviral or antibacterial immunity. Because the pathogenic agent is a misfolded host protein rather than a conventional microorganism, conventional pathogen-recognition and antibody-mediated mechanisms may be insufficient.

Foot-and-Mouth Disease: Rapid Transmission and Immune Memory

Foot-and-mouth disease (FMD) provides an important example of an acute, highly transmissible viral disease in livestock. Its epidemiological importance is amplified by the ability of the virus to spread rapidly between susceptible animals.

From an immunological perspective, FMD highlights the importance of:

- neutralizing antibodies;
- antigenic variation;
- cellular immunity;
- mucosal defence;
- immunological memory; and
- vaccine matching.

The thesis emphasizes that immunological memory is central to protection following infection or vaccination, but rapidly changing viral antigens can reduce the durability or breadth of protection.

This issue is highly relevant to vaccine design. Large-animal models are particularly valuable because vaccine development requires assessment of both immunogenicity and actual protection following pathogen exposure. Large-animal vaccine models can provide physiological and immunological information that may complement data obtained from rodents [41].

Hemorrhagic Septicemia: Rapid Systemic Inflammation

The thesis also describes hemorrhagic septicemia as a rapidly progressing bacterial disease affecting cattle and buffaloes. Infection with pathogenic *Pasteurella multocida* can produce severe septicemia, inflammation and respiratory compromise, with severe cases potentially progressing rapidly to death.

This disease is particularly relevant to the concept of acute inflammatory collapse.

Bovine Tuberculosis: Immunity, Persistence and Zoonotic Importance

Bovine tuberculosis, primarily caused by *Mycobacterium bovis*, provides a valuable example of chronic host–pathogen interaction. The thesis describes involvement of cattle, buffaloes, deer and other animals and emphasizes its zoonotic significance.

The disease demonstrates how pathogens can persist despite substantial cellular immune activation. Granulomatous inflammation can restrict infection but may also contribute to tissue pathology.

Bovine tuberculosis has particular translational importance because livestock research has historically contributed to understanding mycobacterial infection, diagnostics and vaccination. Large-animal research can therefore provide reciprocal benefits to both veterinary and human medicine [42]. The comparison demonstrates that immune activation is not synonymous with protection. In some diseases, effective immunity eliminates the pathogen; in others, immune activation restricts but does not eradicate infection; and in severe disease, excessive immune activity may itself become a major contributor to pathology.

Immunological Memory, Vaccination and Species-Specific Protection

Immunological memory represents one of the most important protective properties of adaptive immunity. Following primary antigen exposure, subsets of B and T lymphocytes develop into memory cells capable of responding rapidly following re-exposure.

The thesis emphasizes that memory B and T cells provide long-term protection following infection or immunization.

Large animals are particularly important for vaccine research because vaccine efficacy depends not only on antibody production but also on the quality, duration and functional breadth of immune responses.

Large-animal models are increasingly recognized as valuable for vaccine development because they can reproduce aspects of immune anatomy, physiology and disease that may be difficult to reproduce in rodents [43].

Table 4: Comparative Immunological Features of Major Diseases.

Disease	Principal host(s)	Dominant disease pattern	Major immune mechanism	Major pathological consequence	Key translational lesson
BLV infection	Cattle	Persistent viral infection	Immune modulation/persistence	Lymphoproliferation and chronic disease	Chronic infection and immune exhaustion
ASF	Swine	Acute systemic viral disease	Innate immune dysregulation	Lymphoid depletion, vascular injury, organ dysfunction	Immunopathology and host-directed intervention
BRD	Cattle	Respiratory disease complex	Mucosal and inflammatory immunity	Lung inflammation and impaired respiration	Respiratory immunology
CWD	Deer and related cervids	Progressive neurodegeneration	Limited conventional immune recognition	Prion accumulation and neurological damage	Protein-misfolding diseases
FMD	Cattle, pigs, sheep and others	Acute viral infection	Neutralizing antibodies and cellular immunity	Vesicular disease and transmission	Vaccine-induced protection
Hemorrhagic septicemia	Cattle/buffalo	Acute bacterial septicemia	Innate inflammation	Vascular/systemic injury	Rapid inflammatory collapse
Bovine tuberculosis	Cattle and other mammals	Chronic infection	Cell-mediated immunity	Granulomatous tissue injury	Zoonotic infection and vaccine development

Large Mammals as Translational Models for Human Disease

One of the most important implications of comparative immunology is its ability to bridge basic immunological discovery and clinical translation.

The thesis emphasizes similarities between animal and human disease mechanisms, including similarities between bovine tuberculosis and human tuberculosis and between inflammatory responses in swine viral infections and severe human viral disease.

Modern literature similarly concludes that large and agricultural animals contribute to understanding infectious diseases, antibody production, vaccines, transplantation and immunotherapies.

Advantages of large-animal models

Large mammals provide several potential advantages:

1. greater physiological similarity to humans for selected systems;
2. larger blood and tissue volumes for longitudinal sampling;
3. clinically relevant disease manifestations;
4. similarity in some anatomical and immunological structures;
5. naturally occurring diseases;
6. better opportunities for repeated clinical monitoring;
7. greater relevance for certain vaccine studies; and
8. opportunities to study long-term disease progression.

However, large-animal models are not universally superior. Species-specific immune differences remain important, and no animal model reproduces the entirety of human immunity. Contemporary reviews explicitly emphasize that model selection must consider species- and tissue-specific immune [44].

Limitations and Challenges in Comparative Large-Mammal Immunology

Despite their scientific value, several limitations must be considered before translating findings between species.

Species-specific immune architecture

A pathway that produces protection in one species may have a different function in another. Therefore, evolutionary adaptations should not be assumed to be directly transferable to humans.

Limited availability of species-specific reagents

Compared with mice and humans, large-animal immunology still has fewer validated antibodies, cytokine reagents and standardized assays. Recent reviews identify this reagent gap as an important limitation, although the situation is improving.

Genetic heterogeneity

Outbred livestock populations may display substantial genetic variation. While this can make experiments more biologically realistic, it can also increase experimental variability.

Cost and infrastructure

Large animals require greater housing, veterinary care, biosafety infrastructure and financial resources than rodents.

Ethical considerations

The scientific value of large-animal studies must always be balanced against animal welfare considerations. Experimental design should therefore follow the principles of reduction, refinement and replacement wherever scientifically possible.

Difficulty of extrapolation

An immune adaptation that benefits an elephant, camelid or bat may not necessarily produce the same outcome in humans. Translation therefore requires mechanistic validation rather than superficial analogy [45].

Future Perspectives: From Comparative Immunology to Evolution-Inspired Therapeutics

The central opportunity emerging from this review is to transform comparative immunology from an observational discipline into a mechanism-discovery platform.

The thesis concludes that molecular biomarkers, immune-modulation strategies and advanced therapeutic approaches may improve disease prevention and treatment [46].

Conclusion

Large mammals represent an important and underutilized source of information for understanding the biological mechanisms underlying lethal disease and survival. The thesis demonstrates that although mammals share fundamental innate and adaptive immune mechanisms, large species have developed distinctive immunological adaptations shaped by body size, metabolism, habitat, pathogen exposure and evolutionary history.

The analysis further demonstrates that mortality cannot be explained solely by pathogen virulence. Disease outcome depends on the balance between pathogen replication and host immune regulation. Excessive inflammatory signalling, immune exhaustion, programmed cell death, mitochondrial dysfunction, oxidative stress and tissue injury can transform an initially protective immune response into a major contributor to disease severity.

At the same time, large mammals provide remarkable examples of naturally evolved protection. Elephants demonstrate enhanced mechanisms of tumour surveillance; camelids have evolved heavy-chain-only antibodies that have become the foundation of nanobody technology; and bats provide important models for investigating antiviral tolerance and controlled inflammation.

The central message emerging from comparative immunology is therefore not that one species possesses a universally superior immune system. Rather, different species have evolved different solutions to the biological challenge of maintaining survival in the presence of pathogens, environmental stress and cellular damage.

Decoding these solutions may provide opportunities to develop improved vaccines, immune-modulatory agents, nanobody therapeutics, biomarkers and host-directed therapies. Contemporary research increasingly supports the value of large animals in infectious disease, vaccination and translational immunology.

Thus, comparative immunology of large mammals should be regarded not merely as a veterinary research discipline but as an evolution-inspired platform for discovering mechanisms of disease resistance, disease tolerance and therapeutic innovation.

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Conflict of Interest

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Ethical Approvals

This study does not involve experiments on animals or human subjects.

References

1. Roth JA, Tuggle CK. Livestock models in translational medicine. ILAR J. 2015;56(1):1-6. doi:10.1093/ilar/ilv011.
2. Gerdts V, Wilson HL, Meurens F, van Drunen Littel-van den Hurk S, Wilson D, Walker S, et al. Large animal models for vaccine development and testing. ILAR J. 2015;56(1):53-62. doi:10.1093/ilar/ilv009.
3. Rajao DS, Vincent AL. Swine as a model for influenza A virus infection and immunity. ILAR J. 2015;56(1):44-52. doi:10.1093/ilar/ilv002.
4. Greenlee JJ, Greenlee MHW. The transmissible spongiform encephalopathies of livestock. ILAR J. 2015;56(1):7-25. doi:10.1093/ilar/ilv008.
5. Waters WR, Palmer MV. Mycobacterium bovis infection of cattle and white-tailed deer: translational research of relevance to human tuberculosis. ILAR J. 2015;56(1):26-43. doi:10.1093/ilar/ilv001.
6. Jensen JL, et al. Immune relevant animal models: opportunities and challenges. ILAR J. 2018;59(3):209-211. doi:10.1093/ilar/ily030.
7. Van de Walle GR, Harman RM. Contributions of large and agricultural animal models to immunology. J Immunol. 2025;214(10):2494-2503. doi:10.1093/jimmun/vkaf119.
8. Ackermann MR, Derscheid R, Roth JA. Innate immunology of bovine respiratory disease. Vet Clin North Am Food Anim Pract. 2010;26(2):215-228. doi:10.1016/j.cvfa.2010.03.001.
9. Ellis JA. The immunology of the bovine respiratory disease complex. Vet Clin North Am Food Anim Pract. 2001;17(3):535-550. doi:10.1016/S0749-0720(15)30006-9.
10. McGill JL, Sacco RE. The immunology of bovine respiratory disease: recent advancements. Vet Clin North Am Food Anim Pract. 2020;36(2):333-348. doi:10.1016/j.cvfa.2020.03.002.
11. Caswell JL. Failure of respiratory defenses in the pathogenesis of bacterial pneumonia of cattle. Vet Pathol. 2014;51(2):393-409. doi:10.1177/0300985813502821.
12. Frie MC, Coussens PM. Bovine leukemia virus: a major silent threat to proper immune responses in cattle. Vet Immunol Immunopathol. 2015;163(3-4):103-114. doi:10.1016/j.vetimm.2014.11.014.
13. Pollock J, McNair J, Welsh MD, Girvin RM, Kennedy HE, Mackie DP, et al. Immune responses in bovine tuberculosis. Tuberculosis (Edinb). 2001;81(1-2):103-107. doi:10.1054/tube.2000.0258.
14. Blanco FC, Sabio y Garcia J, Bigi F. Recent advances in non-specific immune memory against bovine tuberculosis. Comp Immunol Microbiol Infect Dis. 2021;75:101615. doi:10.1016/j.cimid.2021.101615.
15. Shivachandra SB, Viswas KN, Kumar AA. A review of hemorrhagic septicemia in cattle and buffalo. Anim Health Res Rev. 2011;12(1):67-82. doi:10.1017/S146625231100003X.
16. Wilson BA, Ho M. Pasteurella multocida: from zoonosis to cellular microbiology. Clin Microbiol Rev. 2013;26(3):631-655. doi:10.1128/CMR.00024-13.
17. Wu L, Yang B, Yuan X, Hong J, Peng M, Chen JL, et al. Regulation and evasion of host immune response by African swine fever virus. Front Microbiol. 2021;12:698001. doi:10.3389/fmicb.2021.698001.
18. Wang Y, Kang W, Yang W, Zhang J, Li D, Zheng H. Structure of African swine fever virus and associated molecular mechanisms underlying infection and immunosuppression: a review. Front Immunol. 2021;12:715582. doi:10.3389/fimmu.2021.715582.
19. Galindo-Cardiel I, et al. African swine fever virus infection and cytokine response in vivo: an update. Viruses. 2023;15(1):165. doi:10.3390/v15010165.
20. Niu S, et al. Innate immune escape and adaptive immune evasion of African swine fever virus: a review. Virology. 2023;587:109878. doi:10.1016/j.virol.2023.109878.
21. Franzoni G, Graham SP, Dei Giudici S, Oggiano A. Porcine dendritic cells and macrophages: deciphering their role in African swine fever virus infection. Front Microbiol. 2019;10:2970. doi:10.3389/fmicb.2019.02970.
22. Dixon LK, Gaudreault NN, Fullen JR, et al. African swine fever virus pathogenesis and immunity. Annu Rev Anim Biosci. 2020;8:221-243.
23. Gaudreault NN, Madden DW, Wilson WC, Trujillo JD, Richt JA. African swine fever virus: an emerging DNA arbovirus. Front Vet Sci. 2020;7:215.
24. Peng J, Yi J, Yang W, Ren J, Wen Y, Zheng H, et al. Advances in foot-and-mouth disease virus proteins regulating host innate immunity. Front

Microbiol. 2020;11:2046. doi:10.3389/fmicb.2020.02046.
25. Rodríguez-Habibe I, Celis-Giraldo C, Patarroyo ME, Avendaño C, Patarroyo MA. A comprehensive review of the immunological response against foot-and-mouth disease virus infection and its evasion mechanisms. Vaccines (Basel). 2020;8(4):764. doi:10.3390/vaccines8040764.
26. Peng JM, Yi J, Yang W, et al. Molecular mechanisms of immune escape for foot-and-mouth disease virus. Pathogens. 2020;9(9):729. doi:10.3390/pathogens9090729.
27. Pérez-Martín E, Sobrino F, et al. Use of IFN-based biotherapeutics to harness the host against foot-and-mouth disease. Front Vet Sci. 2020;7:465. doi:10.3389/fvets.2020.00465.
28. Alexandersen S, Zhang Z, Donaldson AI, Garland AJM. The pathogenesis and diagnosis of foot-and-mouth disease. J Comp Pathol. 2003;129(1):1-36. doi:10.1016/S0021-9975(03)00041-0.
29. Greenhalgh P, Schutta C, et al. Chronic wasting disease of cervids: current knowledge and future perspectives. Annu Rev Anim Biosci. 2015;3:305-325. doi:10.1146/annurev-animal-022114-111001.
30. Otero A, Duque Velásquez C, Aiken J, McKenzie D. Chronic wasting disease: a cervid prion infection looming to spillover. Vet Res. 2021;52:115. doi:10.1186/s13567-021-00986-y.
31. Haley NJ, Hoover EA. Chronic wasting disease of cervids: current knowledge and future perspectives. Annu Rev Anim Biosci. 2015;3:305-325. doi:10.1146/annurev-animal-022114-111001.
32. Mandl JN, Schneider C, Schneider DS, Baker ML. Going to bat(s) for studies of disease tolerance. Front Immunol. 2018;9:2112. doi:10.3389/fimmu.2018.02112.
33. Irving AT, Ahn M, Goh G, Anderson DE, Wang LF. Lessons from the host defences of bats, a unique viral reservoir. Nature. 2021;589:363-370. doi:10.1038/s41586-020-03128-0.
34. Wang LF, Gamage AM, Chan WOY, Hiller M, Teeling EC. Decoding bat immunity: the need for a coordinated research approach. Nat Rev Immunol. 2021;21:269-271. doi:10.1038/s41577-021-00523-0.
35. Zhang G, Cowled C, Shi Z, Huang Z, Bishop-Lilly KA, Fang X, et al. Comparative analysis of bat genomes provides insight into the evolution of flight and immunity. Science. 2013;339(6118):456-460. doi:10.1126/science.1230835.
36. Gamage AM, Ahn M, et al. Immunological features of bats: resistance and tolerance to emerging viruses. Trends Immunol. 2024;45(3):198-210.
37. Mandl JN, Schneider DS, Schneider C, Baker ML. Going to bat(s) for studies of disease tolerance. Front Immunol. 2018;9:2112. doi:10.3389/fimmu.2018.02112.
38. Hamers-Casterman C, Atarhouch T, Muyldermans S, Robinson G, Hamers C, Songa EB, et al. Naturally occurring antibodies devoid of light chains. Nature. 1993;363:446-448. doi:10.1038/363446a0.
39. Harmsen MM, De Haard HJ. Properties, production, and applications of camelid single-domain antibody fragments. Appl Microbiol Biotechnol. 2007;77(1):13-22. doi:10.1007/s00253-007-1142-2.
40. Muyldermans S. Nanobodies: natural single-domain antibodies. Annu Rev Biochem. 2013;82:775-797. doi:10.1146/annurev-biochem-063011-092449.
41. Jovčevska I, Muyldermans S. The therapeutic potential of nanobodies. BioDrugs. 2020;34(1):11-26. doi:10.1007/s40259-019-00392-z.
42. Abegglen LM, Caulin AF, Chan A, Lee K, Robinson R, Campbell MS, et al. Potential mechanisms for cancer resistance in elephants and comparative cellular response to DNA damage in humans. JAMA. 2015;314(17):1850-1860. doi:10.1001/jama.2015.13134.
43. Sulak M, Fong L, Mika K, Chigurupati S, Yon L, Mongan NP, et al. TP53 copy number expansion is associated with the evolution of increased body size and an enhanced DNA damage response in elephants. Elife. 2016;5:e11994. doi:10.7554/eLife.11994.
44. Pessier AP, Stern JK, Witte CL. TP53 gene and cancer resistance in elephants. JAMA. 2016;315(16):1789. doi:10.1001/jama.2016.0449.
45. Caulin AF, Maley CC. Peto's Paradox: evolution's prescription for cancer prevention. Trends Ecol Evol. 2011;26(4):175-182. doi:10.1016/j.tree.2011.01.002.
46. Peto R. Epidemiology, multistage models, and short-term mutagenicity tests. Int J Epidemiol. 1977;6(2):179-184. doi:10.1093/ije/6.2.179.