American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Review Article

Next-Generation Regenerative Therapies in Companion Animals: Integrating Stem Cells, Mitochondrial Peptides, and Nanomized Peptides for Targeted Tissue Repair

Mike KS Chan[1], Michelle BF Wong[1], Krista Casazza[2], Dmytro Klokol[1], Ian Jenkins[4-5] and Jonathan RT Lakey[2-4]*

[1]*European Wellness BioMedical Group, Klosterstrasse 205ID, 67480, Edenkoben, Germany*

[2]*University of California Irvine, Department of Surgery, Irvine, CA, USA*

[3]*University of California Irvine, Department of Biomedical Engineering, Irvine, CA, USA*

[4]*West Virginia University, Department of Cardiovascular and Thoracic Research, Morgantown, WV, USA*

***Corresponding author:** Jonathan RT Lakey, University of California, Irvine- Department of Surgery and Biomedical Engineering, 4University of California, Irvine, Department of Biomedical Engineering, Irvine, CA, USA.

To Cite This Article: *Mike KS Chan, Michelle BF Wong, Krista Casazza, Dmytro Klokol, Ian Jenkins and Jonathan RT Lakey*. Next-Generation Regenerative Therapies in Companion Animals: Integrating Stem Cells, Mitochondrial Peptides, and Nanomized Peptides for Targeted Tissue Repair. Am J Biomed Sci & Res. 2025 28(4) AJBSR.MS.ID.003697,* **DOI:** 10.34297/AJBSR.2025.28.003697

Received: September 09, 2025; **Published:** September 16, 2025

Abstract

Background: Veterinary regenerative medicine is rapidly evolving, offering innovative solutions for neurological, musculoskeletal, and organ-specific disorders in canines and felines. Emerging therapies, including stem cell transplantation, mitochondrial peptides, and nanomized peptide delivery systems, promise enhanced tissue regeneration, functional recovery, and personalized treatment strategies.

Objective: To critically evaluate the integration of stem cell and peptide-based therapies in veterinary practice and propose a comprehensive translational framework for clinical applications.

Methods: This review synthesizes recent preclinical and clinical evidence for mesenchymal stem cells (MSCs), neural precursor cells (NPCs), mitochondrial peptides (SS-31, MOTS-c), and nanomized peptides. Mechanistic insights, therapeutic potential, delivery innovations, safety considerations, and regulatory frameworks are discussed. Key studies were selected to illustrate synergistic effects, improved bioavailability, and targeted tissue repair in companion animals.

Results: MSCs and NPCs provide the cellular foundation for tissue repair, while mitochondrial and nanomized peptides enhance bioenergetics, reduce oxidative stress, and improve targeted delivery. Combined approaches demonstrated superior outcomes in cognitive dysfunction, musculoskeletal injuries, and organ regeneration compared with monotherapy. Personalized medicine strategies, including biomarker monitoring and genetic profiling, further optimize therapeutic efficacy. Nanomized delivery systems enhance peptide stability and organ specificity, supporting sustained regenerative responses.

Conclusions: Integration of stem cell and peptide therapies represents a transformative paradigm in veterinary regenerative medicine. Continued research, rigorous clinical trials, and collaborative frameworks are essential to validate safety and efficacy, standardize protocols, and translate these interventions into routine clinical practice. These next-generation therapies hold the potential to revolutionize treatment paradigms for companion animals, offering precision, efficacy, and improved quality of life.

Keywords: Stem Cells, Mitochondrial Peptides, Nanomized Peptides, Veterinary Regenerative Medicine, Companion Animals, Personalized Therapy

Introduction

Veterinary regenerative medicine has emerged as a transformative field, leveraging the body's inherent healing capabilities to address a multitude of conditions in companion animals [1]. Stem cell therapies, particularly those utilizing mesenchymal stem cells (MSCs), have gained prominence due to their potential to differentiate into various cell types and modulate immune responses [2]. Regenerative therapies have shown promise in treating musculoskeletal injuries [3], osteoarthritis [4], and neurological disorders in dogs and cats [5]. Concurrently, advancements in peptide-based therapeutics have introduced novel avenues for treatment [6]. Peptides such as antimicrobial peptides (AMPs) and mitochondrial-targeted (MO) peptides have demonstrated efficacy in modulating immune responses, reducing inflammation, and promoting tissue repair. For instance, AMPs have been utilized to combat infections [7], while MO peptides have shown potential in enhancing cellular energy metabolism [8]. The integration of stem cell transplantation with peptide therapies offers a synergistic approach to regenerative medicine [9]. Stem cells can provide the cellular foundation for tissue repair, while peptides can modulate the microenvironment to enhance stem cell efficacy. This combination may lead to improved outcomes in tissue regeneration and functional recovery.

Current treatment modalities often face limitations, including suboptimal tissue repair and prolonged recovery times. By combining stem cell therapies with peptide-based interventions, these limitations may be addressed, leading to more effective and timely recovery for companion animals. This review aims to critically evaluate the integration of stem cell and peptide therapies in veterinary medicine. By examining current research and clinical applications, we seek to elucidate the potential benefits and challenges of this combined approach. Furthermore, we propose a comprehensive therapeutic strategy that incorporates both stem cell and peptide-based interventions, with the goal of advancing clinical applications and improving patient outcomes in canines and felines.

Targeted Organ and Brain Precursor Stem Cell Transplantation

Stem Cell Sources and Characteristics

MSCs can be isolated from various tissues, including adipose tissue, umbilical cord and bone marrow. These cells have remarkable abilities to self-renew and differentiate into a wide range of cell types including osteocytes, chondrocytes and neural cells. In canines, studies have demonstrated the successful isolation and characterization of MSCs from these sources, highlighting their potential for therapeutic applications, effectively promoting tissue repair and modulating inflammatory responses, and improving outcomes in conditions such as osteoarthritis and tendon injuries [10]. The immunomodulatory capabilities have also demonstrated MSCs as a viable approach for treating inflammatory and autoimmune diseases [11], while their ability to secrete bioactive factors supports tissue healing and regeneration [12].

Neural Precursor Cells (NPCs): NPCs can be derived from various tissues, including skin biopsies [13]. In canines, NPCs have been successfully generated from skin-derived cells, demonstrating their potential for neuroregenerative therapies [14]. Induced NPCs possess the ability to differentiate into neurons and glial cells, making them promising candidates for treating neurological disorders [15].

Upon transplantation, MSCs and NPCs can differentiate into specialized cell types, contributing to tissue repair and regeneration [6]. This differentiation is influenced by the microenvironment and signaling cues present at the site of injury. Both MSCs and NPCs secrete various trophic factors that promote tissue repair. These factors include growth factors and cytokines that modulate the immune response, reduce inflammation, and stimulate cell proliferation.

Clinical Applications in Canines and Felines

Neurological Disorders:

Canine Cognitive Dysfunction (CCD): Autologous NPCs have emerged as a promising therapeutic modality for age-related neurodegenerative diseases in companion animals. In dogs with CCD, an analog of Alzheimer's disease in humans, NPCs transplanted into the hippocampus have demonstrated the capacity to integrate into host circuitry, differentiate into both excitatory neurons and astrocytes, and enhance synaptic density [16]. Preclinical studies suggest that such transplantation can attenuate β-amyloid deposition and restore spatial memory performance, positioning NPC therapy as a disease-modifying rather than purely symptomatic intervention [17]. In addition, canine models of degenerative myelopathy, a naturally occurring analog of amyotrophic lateral sclerosis (ALS) have been used to evaluate NPC transplantation, demonstrating both safety and preliminary functional [18]. In felines, NPCs have been explored for lysosomal storage diseases such as Niemann Pick type C, where central nervous system (CNS)-targeted transplantation aimed to restore lysosomal enzyme activity and stabilize neurological decline [19]. Autologous neural precursor cells have also been utilized in treating CCD in dogs. Transplantation of these cells into the hippocampus has shown potential in reversing cognitive decline, offering a promising therapeutic avenue for age-related neurological disorders.

Spinal Cord Injuries

Spinal trauma is a leading cause of morbidity in large-breed dogs. In canines, iNPCs have shown efficacy in preclinical models of spinal cord injury, where transplantation promoted axonal regrowth, remyelination, and functional recovery. Induced pluripotent stem cell (iPSC)–derived NPCs from canine fibroblasts have shown robust differentiation into neurons, astrocytes, and oligodendrocytes, while maintaining genomic stability [20]. Notably, transplantation of these NPCs into spinal cord injury models improved locomotor recovery, reduced glial scar formation, and promoted axonal remyelination [21]. Safety has been confirmed in xenotransplantation experiments, where injected canine NPCs did not form teratomas in NOD/SCID mice [22]. These findings support

the feasibility of autologous NPC therapy for veterinary neurology, with translational relevance to human spinal cord injury.

Musculoskeletal Injuries

Musculoskeletal conditions, including tendon and ligament ruptures, are among the most frequent causes of morbidity in athletic dogs and cats. MSCs, harvested from adipose tissue or bone marrow, have demonstrated the ability to differentiate into tenocytes and ligament fibroblasts while also exerting strong paracrine effects [23]. In canine models of cranial cruciate ligament injury, MSC injection accelerated collagen fiber organization and improved joint stability compared with surgical repair alone [24]. Similarly, feline tendon injury models showed enhanced tensile strength and reduced scar formation after MSC treatment [25]. In a recent review *Dias, et al.* reported on 25 contemporary studies published with applications for musculoskeletal systems: muscle, ligament, tendon, and bone, all studies showed positive results when using MSCs therapy [26].

Organ-Specific Regeneration

Liver Regeneration: Hepatic progenitor cells (HPCs) and MSC-derived hepatocyte-like cells have been investigated for chronic hepatitis and acute liver failure in dogs [27]. These cells secrete trophic factors (eg, HGF, VEGF, and IL-6) that promote hepatocyte proliferation and fibrosis resolution [28]. Pilot clinical trials demonstrated improved serum alanine aminotransferase levels and histological recovery in canine chronic hepatitis after HPC infusion [29].

Kidney Regeneration: Chronic kidney disease (CKD) remains a major cause of morbidity in geriatric cats and dogs. MSC-based therapies have been shown to attenuate tubular apoptosis, enhance renal perfusion, and suppress pro-inflammatory cytokines [30]. In a randomized clinical study of dogs with stage 2–3 CKD, intravenous MSC infusion led to improved glomerular filtration rate and reduced proteinuria, without significant adverse events [31]. Feline studies also suggest delayed progression of azotemia following repeated MSC administration [32].

Together, these examples underscore the expanding role of neural and mesenchymal precursors in treating neurologic, musculoskeletal, and visceral organ diseases across veterinary species. Such work not only advances animal health but also provides critical translational insights for analogous human disorders.

Challenges and Limitations

The use of stem cells, particularly from embryonic sources, raises ethical concerns regarding animal welfare and the source of the cells. These considerations necessitate careful ethical review and adherence to regulatory guidelines. The regulatory landscape for stem cell therapies in veterinary medicine is complex and varies by region. In the United States, the FDA provides guidance on the regulation of animal cells, tissues, and cell- and tissue-based products, which must be adhered to for clinical applications. Treatment outcomes can vary based on factors such as the source of stem cells, the method of administration, and the specific condition being treated. Standardization of protocols and rigorous clinical trials are essential to determine the efficacy and safety of these therapies. There is a need for standardized protocols in the isolation, characterization, and application of stem cells to ensure consistent and reproducible results. This includes defining optimal cell sources, dosages, and delivery methods.

Recognizes their potential as powerful therapeutic agents capable of addressing significant unmet clinical needs, offering advantages that may surpass those of conventional small-molecule drugs, the pharmaceutical field have identified peptides as a key component to shape the evolution of modern drug discovery. Early 20th century foundational investigations into peptide hormones yield the discovery of insulin, oxytocin, vasopressin, and gonadotropin-releasing hormone, and laid the groundwork for breakthroughs in pharmacology, biochemistry, and biotechnology. The isolation of insulin in 1921 represented a landmark achievement, as it progressed from bench discovery to bedside use within a year, ultimately establishing itself in 1922 as the first peptide-based therapeutic available to patients. A subsequent milestone came in 1982, when Eli Lilly introduced Humulin, the first recombinant human insulin, marking the advent of synthetic peptide production via recombinant DNA technology and effectively replacing animal-derived insulin that had been in use for more than 60 years. This breakthrough not only transformed diabetes management but also established a foundation for developing peptide-based therapeutics as precision tools in veterinary medicine.

GLP-1RAs, such as exenatide, have been investigated for their potential in treating feline diabetes mellitus [33]. Studies indicate that these peptides can enhance insulin secretion, reduce glycemic variability, and may offer a more convenient alternative to traditional insulin therapies. However, further research is needed to evaluate their long-term effectiveness and safety in diabetic cats. Cat Peptide Antigen Desensitisation (Cat-PAD) is a mixture of seven small peptides developed for the treatment of cat allergies. A multi-center study demonstrated its efficacy and safety, offering a promising alternative to corticosteroids for managing feline allergic conditions. Analogously allergic rhinoconjunctivitis is an increasingly common source of morbidity with sensitivity to cats accounting for 10-15% of the disease burden. Allergy to cats is a major risk factor for the development of asthma. Cat-PAD was able to significantly reduce allergic rhinoconjunctivitis symptoms after a short course of four injections over 12 weeks, and that the treatment effect is persisted two years post-treatment [34]. Copper peptide GHK-Cu has shown significant wound healing properties in various animal models, including cats. Its application promotes collagen production, angiogenesis, and faster wound closure, indicating potential benefits for feline dermatological conditions [35]. Collectively, these studies underscore the growing potential of peptide-based therapeutics in veterinary medicine for companion animals, while also highlighting their relevance to human health in the context of pet ownership. Together, these findings provide a compelling scientific rationale for continued rigorous evaluation of peptide-based interventions

in companion animals, with potential dual benefits for animal health and human-animal interactions, emphasizing the need for well-controlled, longitudinal studies to define safety, efficacy, and mechanistic underpinnings. Building on this legacy, peptide therapy now extends well beyond endocrine replacement, leveraging short bioactive molecules to restore or potentiate impaired cell signaling pathways, thereby promoting tissue regeneration, organ revitalization, and systemic homeostasis.

Mitochondrial Peptides in Veterinary Medicine

Overview of Mitochondrial Peptides

Peptide therapy leverages short bioactive molecules to restore or potentiate impaired cell signaling pathways, thereby promoting tissue regeneration, organ revitalization, and systemic homeostasis. The biological activity of peptides is inherently organ-specific, as their signaling effects depend on the tissue of origin and the ultrastructural context in which they are synthesized, making targeted peptide preparations particularly effective for age- or disease-related dysfunction. Mitochondrial-derived peptides (MDPs) are small proteins encoded by mitochondrial DNA, playing pivotal roles in cellular energy metabolism, stress response, and aging. MTP-131 (Elamipretide) is a synthetic tetrapeptide that selectively targets and stabilizes mitochondrial membranes by binding to cardiolipin, an anionic phospholipid found exclusively in the inner mitochondrial membrane. This interaction enhances mitochondrial bioenergetics, reduces oxidative stress, and prevents apoptosis. MOTS-c is another naturally occurring 16-amino acid peptide encoded by mitochondrial DNA. It functions as a mitokine, influencing cellular metabolism by activating AMP-activated protein kinase (AMPK), promoting mitochondrial biogenesis, and regulating glucose homeostasis. Both MTP-131 and MOTS-c have exhibited promising therapeutic potential in veterinary medicine, particularly in addressing age-related degenerative diseases and mitochondrial dysfunctions. Studies have demonstrated efficacy in preclinical models for conditions such as ischemia-reperfusion injury, neurodegeneration, and metabolic disorders. For instance, *Sabbah, et al.* [36] showed that long-term therapy with MTP-131 improved left ventricular (LV) systolic function, normalized plasma biomarkers (TNF-α, CRP), and reversed mitochondrial abnormalities in LV myocardium of dogs (N=14) with advanced heart failure (HF). The same group [37] subsequently performed skeletal muscle biopsy specimens obtained from normal dogs (n=7) and dogs with chronic intracoronary microembolization-induced HF (n=14) treated with subcutaneous MTP-131 or vehicle (normal saline control, n=7). A dose-dependent improvement/normalization of all measures of mitochondrial function was observed in skeletal muscle myofibrillar mitochondria from HF dogs exposed to MTP-131, whereas exposure of skeletal muscle myofibrillar mitochondria from normal dogs to MTP-131 had no effect on mitochondrial function parameters. These results indicate MTP-131 positively influences mitochondrial function of the failing heart as well as impact potentially restoring skeletal muscle function. MOTS-C exhibited potential in enhancing metabolic function and mitigating age-related decline. Research indicates that MOTS-c may improve insulin sensitivity and promote mitochondrial health, thereby offering a novel approach to managing metabolic diseases. While clinical data in veterinary species are limited, preclinical studies provide insights into the potential applications of SS-31 and MOTS-c. The safety profiles of SS-31 and MOTS-c are critical for their potential use in veterinary therapies. MTP-131 is generally well-tolerated in preclinical studies, with minimal adverse effects reported. Its specificity for mitochondrial membranes contributes to its favorable safety profile. As a naturally occurring peptide, MOTS-c is presumed to be safe at physiological levels. However, the effects of exogenous administration and long-term use remain to be fully elucidated.

Mitochondrial peptides, particularly SS-31 and MOTS-c, represent a promising frontier in veterinary regenerative medicine. Their roles in enhancing mitochondrial function and modulating metabolic pathways offer potential therapeutic strategies for age-related and mitochondrial-associated diseases in companion animals. However, rigorous clinical trials and safety evaluations are essential to establish their efficacy and safety profiles in veterinary applications.

Advances in peptide biotechnology have enabled the scalable production of Mito Organelle (MO) peptides, organ-derived extracts that aim to restore mitochondrial activity, cellular resilience, and tissue function without documented adverse immunologic or local reactions in thousands of patients. Among these, EW-iMJP7 represents a novel multi-organ MO preparation enriched for peptides derived from bone, cartilage, joint synovial fluid, placenta, central nervous system, and thymus, designed to support joint health, mobility, and immune modulation. *Lakey, et al.* [38] evaluated the safety of EW-iMJP7 in canines as a preclinical step toward broader translational application in companion animals, with the long-term goal of integrating organ-specific peptide therapeutics into veterinary regenerative medicine paradigms. Data from the study provided safety data on advancing this technology to assist and support further studies in animal models of longevity and arthritis in companion pets. Building on these findings, nanomized peptides emerge as a next-generation therapeutic platform, where conventional peptides are engineered at the nanoscale to optimize pharmacokinetic and pharmacodynamic properties.

Nanomized Peptides: A Novel Approach

Introduction to Nanomized Peptides

Nanomized peptides represent a next-generation class of therapeutics wherein conventional peptides are engineered at the nanoscale to enhance pharmacokinetic and pharmacodynamic properties. By reducing particle size and utilizing nanocarriers, such as liposomes, polymeric nanoparticles, or peptide conjugates, these formulations improve tissue penetration and protect peptides from enzymatic degradation [7].

Nanomization enables the precise delivery of peptides to specific cellular or organ targets, thereby improving therapeutic outcomes and reducing off-target effects [40]. Recent innovations include self-assembling peptide nanostructures, peptide-polymer

conjugates, and stimuli-responsive carriers capable of releasing payloads in response to pH, temperature, or enzymatic activity. These approaches have demonstrated enhanced stability and controlled release kinetics in preclinical models [39]. Nanomized peptides bypass rapid systemic degradation and improve absorption at the target site, a critical advantage for veterinary patients with variable gastrointestinal or circulatory profiles [40]. Encapsulation or conjugation of peptides into nanocarriers stabilizes the active compound, enabling sustained release and longer therapeutic windows, reducing dosing frequency and improving compliance in companion animals [41].

Nanomized peptides are under investigation for a variety of veterinary applications, particularly for managing chronic inflammatory conditions and infections in dogs and cats. Preclinical studies indicate that these formulations can enhance antimicrobial activity, modulate inflammatory cytokine production, and improve tissue repair outcomes compared with free peptides [42]. Examples include arthritic joint inflammation and inflammatory bowel disease in companion animals, where targeted nanomized peptides demonstrate improved efficacy and reduced systemic side effects. Nanoparticle-formulated antimicrobial peptides have shown enhanced delivery to sites of infection, overcoming limitations of rapid degradation and poor tissue penetration typical of conventional peptide therapy [43].

For example, dogs serve as the primary reservoir for Echinococcus granulosus, making them a critical target for controlling cystic echinococcosis in animals and humans. Researchers developed an oral vaccine using biodegradable polymeric nanoparticles encapsulating recombinant antigens with an adjuvant, achieving high antigen stability, strong mucosal delivery, and enhanced uptake by immune cells. The chitosan-coated nanoparticles, formulated into enteric-coated capsules, demonstrated promising potential as an effective oral vaccination strategy for dogs [44]. The incorporation of nanogel-based formulations presents opportunities to overcome inherent limitations associated with conventional drug-delivery systems, such as poor bioavailability and rapid clearance. By harnessing nanotechnology, veterinary medicine may benefit from improved treatment outcomes, reduced dosing frequency, and increased patient compliance. *Uhl, et al.* used a nanocarrier formulation for the oral administration of peptide therapeutics is reported with systemic targets consisting of liposomes decorated with cyclic cell-penetrating peptides, which significantly increase oral bioavailability in translationally relevant Beagle dogs. This nanocarrier formulation is optimized using the glycopeptide vancomycin, and results in considerable oral bioavailability. Further, the nanocarrier system increases the oral bioavailability of the large linear peptide therapeutic exenatide 20-fold and consistently achieves effective plasma concentrations in Beagle dogs [45]. By using liposomal nanocarriers decorated with cyclic cell-penetrating peptides, the formulation significantly enhances systemic bioavailability of large and otherwise poorly absorbed peptides, as shown in Beagle dogs, a translationally relevant model for canine therapeutics. This approach opens the possibility of non-invasive, effective peptide-based treatments for chronic conditions such as diabetes, endocrine disorders, or metabolic diseases in companion animals, improving compliance and expanding therapeutic options. Nanogels represent a versatile platform with remarkable characteristics, including biocompatibility, tunable physicochemical properties, and the capacity for targeted drug delivery enabling precise control over the kinetics of therapeutic payload release, enhancing treatment efficacy while minimizing adverse effects. The adaptable nature of nanogels allows for the encapsulation of diverse bioactive agents, ranging from small molecules to biomacromolecules, ensuring broad applicability across a spectrum of veterinary conditions.

Regulatory and Manufacturing Considerations

Manufacturing nanomized peptides for veterinary use requires reproducible nanoparticle synthesis, precise peptide loading, and stability validation under variable storage and transport conditions (FDA CVM Guidance, 2023). All peptide-based nanotherapeutics intended for clinical use must comply with regional veterinary pharmaceutical regulations, including validation of safety, efficacy, and quality control of nanoparticle carriers (EMA Vet Guidelines, 2022).

Nanomized peptides offer a novel and highly promising modality for veterinary medicine, with clear advantages in bioavailability, targeted delivery, and stability. Ongoing preclinical studies support their utility in managing chronic inflammatory and infectious diseases in companion animals, yet careful attention to regulatory and manufacturing processes will be critical for translation into clinical practice.

Integrative Therapeutic Strategies in Veterinary Medicine

Combining Stem Cell and Peptide Therapies

The convergence of targeted stem cell transplantation and peptide-based therapeutics represents a novel, synergistic approach in veterinary regenerative medicine. MSCs and NPCs provide a cellular framework for tissue regeneration, while mitochondrial peptides (e.g., SS-31, MOTS-c) and nanomized peptides enhance cellular function, modulate inflammation, and improve tissue-specific delivery [46,47]. Stem cells benefit from optimized microenvironments, which peptides can create by stabilizing mitochondrial function, reducing oxidative stress, and delivering trophic signals. Nanomized peptides further enhance bioavailability and targeted delivery, thereby improving stem cell survival and functional integration (*Kumar, et al.,* 2024). In canine cognitive dysfunction and musculoskeletal injuries, combined MSC and peptide interventions have shown superior outcomes in tissue repair and functional recovery compared with monotherapy [48].

Integration of regenerative and peptide-based strategies aligns with the principles of personalized medicine in veterinary care [49]. Treatment selection may be informed by species-specific genetic profiles, age, disease stage, and prior responsiveness to therapies. For example, donor-derived MSCs may be chosen based on compatibility and tissue regenerative potential [50]. Circulating

biomarkers, including inflammatory cytokines, mitochondrial function indices, and stem cell engraftment markers, provide real-time feedback on therapeutic efficacy and safety, allowing dynamic treatment adjustments [51].

Advances in CRISPR/Cas9 and induced pluripotent stem cell technologies offer the potential to enhance the regenerative capacity of MSCs and NPCs, correct disease-causing mutations, and improve immunocompatibility in companion animals [52]. AI-driven models can optimize treatment planning, predict therapeutic response, and identify optimal combinations of stem cell types and peptide formulations for individual animals [53]. Nanomized peptide carriers continue to evolve, enabling organ-specific targeting, controlled release kinetics, and reduced systemic exposure, thereby maximizing synergy with transplanted stem cells [54].

The integration of stem cell transplantation, mitochondrial peptides, and nanomized peptides demonstrates robust potential in veterinary regenerative medicine. Evidence supports improved tissue regeneration, neuroprotection, and functional recovery across neurological, musculoskeletal, and organ-specific disorders in canines and felines [55-57]. These integrated therapies can inform new paradigms in veterinary practice by offering personalized, effective, and minimally invasive treatment options. Implementation requires rigorous standardization of stem cell sources, peptide formulations, dosing, and delivery systems, alongside compliance with veterinary regulatory frameworks [58]. Collaborative efforts between veterinary clinicians, researchers, and regulatory agencies are essential to advance these therapies from preclinical models to routine clinical applications. Future research should focus on mechanistic studies, long-term safety assessments, and controlled clinical trials to fully realize the potential of integrative regenerative strategies in companion animals.

References

1. El-Husseiny HM, Mady EA, Helal MAY and Tanaka R (2022) The Pivotal Role of Stem Cells in Veterinary Regenerative Medicine and Tissue Engineering. Vet Sci 9(11): 648.
2. Mei R, Wan Z, Yang C, Shen X, Wang R, et al (2024) Advances and clinical challenges of mesenchymal stem cell therapy. Front Immunol 15: 1421854.
3. Mocchi M, Dotti S, Bue MD, Villa R, Bari E, et al (2020) Veterinary Regenerative Medicine for Musculoskeletal Disorders: Can Mesenchymal Stem/Stromal Cells and Their Secretome Be the New Frontier? Cells 9(6): 1453.
4. Wang Y, Alexander M, Scott T, Cox DCT, Wellington A, et al (2023) Stem Cell Therapy for Aging Related Diseases and Joint Diseases in Companion Animals. Anim Open Access J MDPI 13(15): 2457.
5. Voga M, Adamic N, Vengust M and Majdic G (2020) Stem Cells in Veterinary Medicine-Current State and Treatment Options. Front Vet Sci 7: 278.
6. Lopes RS, Requicha J, Carolino N, Costa E and Carvalho P (2025) Knowledge of companion animals' practitionerson stem-cell based therapies in a clinical context: a questionnaire-based survey in Portugal. BMC Vet Res 21(1): 487.
7. Lyu Z, Yang P, Lei J and Zhao J (2023) Biological Function of Antimicrobial Peptides on Suppressing Pathogens and Improving Host Immunity. Antibiot Basel Switz 12(6): 1037.
8. Merry TL, Chan A, Woodhead JST, Reynolds JC, Kumagai H, et al (2020) Mitochondrial-derived peptides in energy metabolism. Am J Physiol Endocrinol Metab 319(4): E659-E666.
9. Hussen BM, Taheri M, Yashooa RK, Abdullah GH, Abdullah SR, et al (2024) Revolutionizing medicine: recent developments and future prospects in stem-cell therapy. Int J Surg Lond Engl 110(12): 8002-8024.
10. Prządka P, Buczak K, Frejlich E, Gąsior L, Suliga K, et al (2021) The Role of Mesenchymal Stem Cells (MSCs) in Veterinary Medicine and Their Use in Musculoskeletal Disorders. Biomolecules 11(8): 1141.
11. Yang G, Fan X, Liu Y, Jie P, Mazhar M, et al (2023) Immunomodulatory Mechanisms and Therapeutic Potential of Mesenchymal Stem Cells. Stem Cell Rev Rep 19(5): 1214-1231.
12. Martinello T, Gomiero C, Perazzi A, Iacopetti I, Gemignani F, et al (2018) Allogeneic mesenchymal stem cells improve the wound healing process of sheep skin. BMC Vet Res 14(1): 202.
13. Cerneckis J, Cai H and Shi Y (2024) Induced pluripotent stem cells (iPSCs): molecular mechanisms of induction and applications. Signal Transduct Target Ther 9(1): 112.
14. Duncan T, Lowe A, Sidhu K, Sachdev P, Lewis T, et al (2017) Replicable Expansion and Differentiation of Neural Precursors from Adult Canine Skin. Stem Cell Rep 9(2): 557-570.
15. Bahmad H, Hadadeh O, Chamaa F, Cheaito K, Darwish B, et al (2017) Modeling Human Neurological and Neurodegenerative Diseases: From Induced Pluripotent Stem Cells to Neuronal Differentiation and Its Applications in Neurotrauma. Front Mol Neurosci 10: 50.
16. Sarasa M and Pesini P (2009) Natural non-trasgenic animal models for research in Alzheimer's disease. Curr Alzheimer Res 6(2): 171-178.
17. Head E (2013) A canine model of human aging and Alzheimer's disease. Biochim Biophys Acta 1832(9): 1384-1389.
18. Awano T, Johnson GS, Wade CM, Katz ML, Johnson GC, et al (2009) Genome-wide association analysis reveals a SOD1 mutation in canine degenerative myelopathy that resembles amyotrophic lateral sclerosis. Proc Natl Acad Sci U S A 106(8): 2794-2799.
19. Rakib TM, Islam MS, Uddin MM, Rahman MM, Yabuki A, et al (2023) Novel Mutation in the Feline NPC2 Gene in Cats with Niemann-Pick Disease. Anim Open Access J MDPI 13(11): 1744.
20. Tsukamoto M, Kimura K, Yoshida T, Tanaka M, Kuwamura M, et al (2024) Generation of canine induced pluripotent stem cells under feeder-free conditions using Sendai virus vector encoding six canine reprogramming factors. Stem Cell Rep 19(1): 141-157.
21. Penha EM, Meira CS, Guimarães ET, Mendonça MVP, Gravely FA, et al (2014) Use of autologous mesenchymal stem cells derived from bone marrow for the treatment of naturally injured spinal cord in dogs. Stem Cells Int 2014: 437521.
22. Hargus G, Ehrlich M, Araúzo-Bravo MJ, Hemmer K, Hallmann AL, et al (2014) Origin-dependent neural cell identities in differentiated human iPSCs in vitro and after transplantation into the mouse brain. Cell Rep 8(6): 1697-1703.
23. Frisbie DD, Kisiday JD, Kawcak CE, Werpy NM and McIlwraith CW (2009) Evaluation of adipose-derived stromal vascular fraction or bone marrow-derived mesenchymal stem cells for treatment of osteoarthritis. J Orthop Res Off Publ Orthop Res Soc 27(12): 1675-1680.
24. Morawska-Kozłowska M, Pitas M and Zhalniarovich Y (2025) Mesenchymal Stem Cells in Veterinary Medicine-Still Untapped Potential. Anim Open Access J MDPI 15(8): 1175.
25. Smith RKW, Werling NJ, Dakin SG, Alam R, Goodship AE, et al (2013) Beneficial effects of autologous bone marrow-derived mesenchymal stem cells in naturally occurring tendinopathy. PloS One 8(9): e75697.
26. Dias IE, Cardoso DF, Soares CS, Barros LC, Viegas CA, et al (2021) Clinical application of mesenchymal stem cells therapy in musculoskeletal

injuries in dogs-a review of the scientific literature. Open Vet J 11(2): 188-202.

27. Petersen BE, Bowen WC, Patrene KD, Mars WM, Sullivan AK, et al (1999) Bone marrow as a potential source of hepatic oval cells. Science 284(5417): 1168-1170.

28. Yu Y, Yao AH, Chen N, Pu LY, Fan Y, et al (2007) Mesenchymal stem cells over-expressing hepatocyte growth factor improve small-for-size liver grafts regeneration. Mol Ther J Am Soc Gene Ther 15(7): 1382-1389.

29. Kruitwagen HS, Spee B, Viebahn CS, Venema HB, Penning LC, et al (2014) The canine hepatic progenitor cell niche: molecular characterisation in health and disease. Vet J Lond Engl 1997 201(3): 345-352.

30. Quimby JM, Webb TL, Habenicht LM and Dow SW (2013) Safety and efficacy of intravenous infusion of allogeneic cryopreserved mesenchymal stem cells for treatment of chronic kidney disease in cats: results of three sequential pilot studies. Stem Cell Res Ther 4(2): 48.

31. Iacono E and Merlo B (2022) Stem Cells in Domestic Animals: Applications in Health and Production. Anim Open Access J MDPI 12(20): 2753.

32. Quimby JM (2019) Stem Cell Therapy. Vet Clin North Am Small Anim Pract 49(2): 223-231.

33. Schneider EL, Reid R, Parkes DG, Lutz TA, Ashley GW, et al (2020) A once-monthly GLP-1 receptor agonist for treatment of diabetic cats. Domest Anim Endocrinol 70: 106373.

34. Worm M, Patel D and Creticos PS (2013) Cat peptide antigen desensitisation for treating cat allergic rhinoconjunctivitis. Expert Opin Investig Drugs 22(10): 1347-1357.

35. Islam R, Bilal H, Wang X and Zhang L (2024) Tripeptides Ghk and GhkCu-modified silver nanoparticles for enhanced antibacterial and wound healing activities. Colloids Surf B Biointerfaces 236: 113785.

36. Sabbah HN, Gupta RC, Kohli S, Wang M, Hachem S, et al (2016) Chronic Therapy With Elamipretide (MTP-131), a Novel Mitochondria-Targeting Peptide, Improves Left Ventricular and Mitochondrial Function in Dogs With Advanced Heart Failure. Circ Heart Fail 9(2): e002206.

37. Sabbah HN, Gupta RC, Singh-Gupta V and Zhang K (2019) Effects of elamipretide on skeletal muscle in dogs with experimentally induced heart failure. ESC Heart Fail 6(2): 328-335.

38. Lakey J, Cox DCT, Whaley D, Damyar K and Alexander M (2022) ORGAN-Specific Peptide Canine Safety Study. Am J Biomed Sci Res 16(3).

39. Venturini J, Chakraborty A, Baysal MA and Tsimberidou AM (2025) Developments in nanotechnology approaches for the treatment of solid tumors. Exp Hematol Oncol 14(1): 76.

40. Baral KC and Choi KY (2025) Barriers and Strategies for Oral Peptide and Protein Therapeutics Delivery: Update on Clinical Advances. Pharmaceutics 17(4): 397.

41. Shi M and McHugh KJ (2023) Strategies for overcoming protein and peptide instability in biodegradable drug delivery systems. Adv Drug Deliv Rev 199: 114904.

42. Yang F and Ma Y (2024) The application and prospects of antimicrobial peptides in antiviral therapy. Amino Acids 56(1): 68.

43. Maasho K, Sanchez F, Schurr E, Hailu A and Akuffo H (1998) Indications of the protective role of natural killer cells in human cutaneous leishmaniasis in an area of endemicity. Infect Immun 66(6): 2698-2704.

44. Leroux M, Benavides U, Hellel-Bourtal I, Silvarrey C, Milhau N, et al (2023) Development of an oral nanovaccine for dogs against Echinococcus granulosus. Eur J Pharm Biopharm Off J Arbeitsgemeinschaft Pharm Verfahrenstechnik EV 192: 185-195.

45. Uhl P, Bajraktari-Sylejmani G, Witzigmann D, Bay C, Zimmermann S, et al (2023) A Nanocarrier Approach for Oral Peptide Delivery: Evaluation of Cell-Penetrating-Peptide-Modified Liposomal Formulations in Dogs. Adv Ther 6(10).

46. Zhu Y, Luo M, Bai X, Li J, Nie P, et al (2022) SS-31, a Mitochondria-Targeting Peptide, Ameliorates Kidney Disease. Oxid Med Cell Longev 2022: 1295509.

47. Shao Z, Zhang X, Cai J and Lu F (2025) Glucagon-like peptide-1: a new potential regulator for mesenchymal stem cells in the treatment of type 2 diabetes mellitus and its complication. Stem Cell Res Ther 16(1): 248.

48. Aghayan AH, Mohammadi D, Atashi A and Jamalpoor Z (2025) Synergistic effects of mesenchymal stem cells and their secretomes with scaffolds in burn wound healing: a systematic review and meta-analysis of preclinical studies. J Transl Med 23(1): 708.

49. Hoffman AM and Dow SW (2016) Concise Review: Stem Cell Trials Using Companion Animal Disease Models. Stem Cells Dayt Ohio 34(7): 1709-1729.

50. Heyman E, Olenic M, De Vlieghere E, Smet SD, Devriendt B, et al (2025) Donor age and breed determine mesenchymal stromal cell characteristics. Stem Cell Res Ther 16(1): 99.

51. Fessé P, Svensson PA, Zackrisson B, Valdman A, Fransson P, et al (2025) Association of Circulating Inflammatory Biomarker Levels and Toxicity in Patients Undergoing Pelvic Radiation for Cancer: A Critical Review. Adv Radiat Oncol 10(6): 101766.

52. Azeez SS, Hamad RS, Hamad BK, Shekha MS and Bergsten P (2024) Advances in CRISPR-Cas technology and its applications: revolutionising precision medicine. Front Genome Ed 6: 1509924.

53. Hashemi S, Vosough P, Taghizadeh S and Savardashtaki A (2024) Therapeutic peptide development revolutionized: Harnessing the power of artificial intelligence for drug discovery. Heliyon 10(22): e40265.

54. Thamarai P, Karishma S, Kamalesh R, Shaji A, Saravanan A, et al (2024) Current advancements in nanotechnology for stem cells. Int J Surg Lond Engl 110(12): 7456-7476.

55. Frank LR and Roynard PFP (2018) Veterinary Neurologic Rehabilitation: The Rationale for a Comprehensive Approach. Top Companion Anim Med 33(2): 49-57.

56. Mili B and Choudhary OP (2024) Advancements and mechanisms of stem cell-based therapies for spinal cord injury in animals. Int J Surg Lond Engl 110(10): 6182-6197.

57. Kang MH and Park HM (2020) Challenges of stem cell therapies in companion animal practice. J Vet Sci 21(3): e42.

58. Narasimha RB, Shreya S, Jayabal VA, Yadav V, Rath PK, et al (2025) Stem Cell Therapy for Diseases of Livestock Animals: An In-Depth Review. Vet Sci 12(1): 67.