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Review Article

# Translational human and equine regenerative medicine in musculoskeletal conditions

L.M. Bosman [a,*], M.G. Logan [a,b], A. Miszewski [b,c], M.S. Pepper [a,c]

[a] Institute for Cellular and Molecular Medicine, and SAMRC Extramural Unit for Stem Cell Research and Therapy, Department of Medical Immunology, Faculty of Health Sciences, University of Pretoria, Pretoria, Gauteng, 0084, South Africa
[b] Novita Biotechnology, Cape Town, Western Cape, 7945, South Africa
[c] Altera Biosciences, Tshwane, Gauteng, 0084, South Africa

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ABSTRACT

Translational regenerative medicine, integrating human and veterinary approaches within the "One Health" framework, increasingly uses horses as models for human musculoskeletal conditions due to shared anatomical and functional features. Osteoarthritis and tendon disorders affect both species, often resulting from high-impact or repetitive strain activities. Regenerative medicine offers therapeutic opportunities by promoting tissue repair and modulating inflammation. Cellular orthobiologics such as mesenchymal stromal/stem cells (MSCs) show promise for treating osteoarthritis and tendon injuries in humans and horses, while non-cellular orthobiologics—including platelet-rich plasma, interleukin-1 receptor antagonist protein, and alpha-2 macroglobulin—provide growth factors and anti-inflammatory molecules that support tissue regeneration. However, challenges remain, including variable product manufacture, inconsistent MSC isolation and characterization protocols (particularly in equine applications), and regulatory or public scepticism toward these therapies. Standardized production methods and improved clinical integration are needed. Combinatory use of cellular and non-cellular orthobiologics offers strong translational potential to improve musculoskeletal repair across species.

## 1. Introduction

In 1976, the concept of "One Medicine" was founded, which subsequently led the World Health Organisation to develop the "One Health" initiative in the early 2000′s [1]. This approach brings researchers and healthcare practitioners together in a collaborative space, allowing for improved health outcomes across species by recognizing the interconnectedness of humans, animals and the environment [2]. The socio-economic component of "One Health" has been integrated into this initiative to further improve outcomes [1,2]. Translational medicine in the context of the "One Health" initiative can be viewed in two ways. First, to use information and insights obtained from one species such as mice, rats, livestock or horses, to inform disease and injury treatment in another e.g. humans; and second, to translate this information into products and services in the commercial space [1].

Use of the "One Health" paradigm for musculoskeletal disorders such as osteoarthritis (OA) has the potential to translate findings in horses to a human context. Horses have been identified as a preferred model for musculoskeletal therapeutic research over the conventional mouse and rat models due to the similarity between equine and human musculoskeletal systems [3]. This involves a complex arrangement of tendons, ligaments, bones, muscles, and joints, which collectively provide the body with structure, support, movement and protection of the viscera [4]. Both horses and humans are prone to musculoskeletal disorders which can lead to comparable conditions including injury and degeneration, which significantly affect the structure, function and cellular architecture of the tissue, potentially resulting in debilitating inflammation, pain, and reduced quality of life [5].

Horses and humans are involved in high intensity and high impact athletic sports/activities, and certain injuries in horses can be directly compared to injuries seen in humans, and vice versa. 86% of equine diseases are musculoskeletal in nature, 37% of which are due to connective tissue trauma [6,7]. Common musculoskeletal pathologies found in competition horses include OA, injuries to the distal deep digital flexor tendon or superficial digital flexor tendon, laminitis, and forelimb suspensory desmitis [8–10]. In humans, musculoskeletal problems are a major societal burden from a social and economic standpoint, in both high- and low-to-middle income countries [11]. Chronic and acute

* Corresponding author.
*E-mail address:* lisamariebosman@gmail.com (L.M. Bosman).

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injuries are common, especially among athletes and workers in physically demanding roles [12]. These injuries include OA and tendinopathies, and often involve the anterior cruciate ligament (ACL), Achilles tendon and rotator cuff [12].

Many musculoskeletal diseases result from high levels of stress placed on specific anatomical compartments. Physical exertion, over extension with abrupt contraction of tendons, and/or overexertion of a tissue due to repeated impact, can lead to loss of function of a limb [13]. The extent of damage is highly dependent on age, and in the case of equine and human athletes, also includes competition level, intensity of exercise and impact, and discipline and/or sport type [14]. For example, tendon fibre rupture predominantly seen in equine racers, eventers and show jumpers, can lead to a sterile inflammatory response as a consequence of cell death, resulting in tendonitis [7,14]. Unfortunately, reinjury rates in the equine musculoskeletal system can be as high as 66%, while muscle-specific reinjury rates in humans range from 12-43% [15,16]. This is due to the complex, multifactorial aetiology of these injuries, which includes tissue specificity, age, genetics, immune system changes and local environment [6,14]. Consequently, a great deal of effort is being directed at identifying novel treatment options including those that may provide a long-term solution.

## 2. Regenerative medicine

Regenerative medicine, one of the key constituents of advanced therapies, is an emerging field that seeks to use the body's natural regenerative abilities to replace, engineer, or regenerate cells and tissues to establish and/or restore normal function [5,17,18]. The two main categories of regenerative medicine are cell-based and non-cellular therapies, referred to as cellular and non-cellular orthobiologics in the context of musculoskeletal injuries. This is an exciting field of research, as it has the potential to provide treatment options for a wide range of orthopaedic diseases and injuries. Most treatments are produced *ex vivo* in both autologous (products isolated from a patient are administered to the same patient) and allogeneic (donor products administered to a different patient) forms [14], with the aim of activating the recipient's inherent somatic reparative processes.

Non-cellular orthobiologics include predominantly blood-derived products and recombinant proteins. Platelet rich plasma (PRP) was first described in 1954 by Kingsley, and only in later years was it used clinically for the treatment of thrombocytopenia (1960s) and in various surgical procedures (1970s) [19]. Its use for the treatment of musculoskeletal conditions and in orthopaedic procedures began in the late 1990s in humans [20], and it was applied in a musculoskeletal veterinary context in the early 2000′s [21]. Research and clinical findings relating to the use of equine PRP has been published in the last decade, and its use as an orthobiologic has been extensively documented. Around the same time, alpha 2 macroglobulin (A2M) and interleukin-1 receptor antagonist protein (IRAP) were identified as possible recombinant protein and autologous blood-derived therapeutics in the early 2000′s [21,22]. Their effects on degenerative joint disorders such as OA and tissue specific healing, have been well described [21,22].

Mesenchymal stromal/stem cells (MSCs), a term coined by Caplan, were first isolated in the 1960s from rat bone marrow and characterized as having "osteogenic potential" and a "fibroblastoid shape" [23]. Their use as cellular orthobiologics began in 1995, when the first MSCs were used *in vivo* in human clinical trials [24]; however, legislation surrounding their use as an advanced medicinal therapy only came into effect in 2001 (The European Directive 2001/83/CE). The first MSC commercial product was authorized for use in human paediatric steroid-refractory acute graft-versus-host disease (Prochymal™) in 2012 [25]. MSC research and clinical application in horses has been more recent, dating from 2003, where they were used for the treatment of superficial digital flexor tendon injuries [26]. Since 2020, over 1,000 human clinical trials have been registered worldwide to investigate the use of MSCs for a range of diseases and disorders including but not limited to OA, Coronavirus Disease 2019 (COVID-19), graft-versus-host disease and inflammatory bowel disease (see clinicaltrials.gov).

### 2.1. Non-cellular orthobiologics

Whole blood is comprised of blood plasma and cells, including red blood cells (erythrocytes), white blood cells (leukocytes), and platelets (thrombocytes) [27]. Blood plasma is the liquid portion of whole blood and excludes cellular components [27,28]. It consists mainly of proteins including albumin, coagulating factors, circulating antibodies, and electrolytes. The main functions of blood plasma are to aid in blood clotting, maintain pH levels, and regulate blood pressure. Bioactive molecules found in cells in the blood exert a range of therapeutic effects by promoting repair and tissue maintenance via angiogenesis, alteration of the inflammatory response, and cell proliferation and differentiation [14]. Blood derivatives contain cytokines and growth factors (GFs) derived from these cells, properties which are particularly valuable in the context of musculoskeletal injury, where the natural healing capacity of the associated tissues is often limited.

PRP is the most widely used blood-derived product for musculoskeletal disease and injury and has been used in research and commercial settings since the late 20th century. PRP is specifically used for tendinopathy and ligament inflammation in both horses and humans. It is isolated via centrifugation from the non-coagulated fluid portion of drawn blood (or via apheresis) and is characterised by increased platelet concentration when compared to the original whole blood sample [29,30]. During primary haemostasis in vascular injury, biologically active molecules, including GFs, are released from degranulated α-granules (intracellular components of platelets) to support wound healing and fibrin clot formation in the early inflammatory phase [31]. *Ex vivo* preparation of PRP results from the degranulation of α-granules as a consequence of centrifugal force, often in combination with calcium chloride salt and activating enzymes such as thrombin, which promote platelet degranulation [32]. When autologous PRP is reintroduced locally through either intra-muscular, intra-articular, or ultrasound guided intra-lesional injection, it promotes tissue repair and cell proliferation due to the variety of bioactive molecules concentrated within the product [29].

PRP generally has a range of GF's such as vascular endothelial growth factor (VEGF) which promotes angiogenesis and regulates endothelial cell longevity and function [30,33,34]; transforming growth factor-α and β (TGF-α & TGF-β) which contribute to cartilage formation, cell expansion, and differentiation [35]; platelet-derived growth factor (PDGF) which regulates endothelial cell migration and proliferation; fibroblast growth factor (FGF) which supports both the proliferation and differentiation of endothelial cells; insulin-like growth factor (IGF) which regulates apoptosis, cartilage cell differentiation, and proliferation [33,34]; interleukin-1 receptor antagonist (IL-1Ra, IRAP) which acts as a potent anti-inflammatory agent by binding to pro-inflammatory molecules; and A2M which helps prevent articular tissue breakdown by attenuation of pro-inflammatory molecules [35].

IRAP is a glycoprotein which competitively binds to both type 1 and 2 interleukin-1 (IL-1) receptor sites, without inducing a detectable intracellular response as a consequence of this interaction [36]. IL-1 is a proinflammatory cytokine that directly contributes to connective tissue – specifically cartilage matrix – degradation, by promoting inflammation post-injury [37]. By binding the IL-1 receptor, IRAP limits mononuclear cell infiltration and inflammatory activation, reducing swelling, tissue damage, and pain [36]. The main method of IRAP production, specifically for musculoskeletal disorders, is through processing of autologous venous blood [38]. The sample is drawn from the patient, generally into a glass tube containing glass beads, stimulating monocytes to produce and secrete IRAP [38]. The sample is incubated for approximately 24 hours, and then centrifuged to separate plasma from cells [38]. The plasma-IRAP solution, often referred to as autologous conditioned serum (ACS) in human orthobiologics, is either injected

locally into a joint or soft tissue, or frozen for later use [38]. By producing an autologous product, there is virtually no risk of an adverse immune response. Autologous IRAP is an increasingly popular veterinary orthobiologic used to treat musculoskeletal injuries and degenerative connective tissue diseases. A small number of private orthopaedic surgeons and sports medicine specialists offer ACS as an unregulated therapeutic in humans.

A2M is another protein produced by autologous blood processing which has demonstrated therapeutic properties. It is a large glycoprotein produced naturally by the liver, and acts as a potent broad-spectrum protease inhibitor [39]. In haemostasis it undergoes a conformational change upon binding to proteases such as thrombin and plasmin, effectively trapping and inactivating them [39]. This reduces proteolytic activity that otherwise would contribute to cartilage degradation and tissue damage, particularly in inflammatory joint conditions [27]. Under sterile conditions, autologous whole blood is centrifuged to separate the plasma containing A2M, from cells [27]. The A2M undergoes ultrafiltration out of the plasma to subsequently concentrate it [27]. Alternative processing systems such as the FDA approved Autologous Platelet Integrated Concentration (APIC) (Cytonics) system use proprietary tangential flow filters to "selectively enrich" plasma with A2M protein [27]. Concentrated A2M is then administered locally via peritendinous or intra-articular injection at the target site [27].

### 2.2. Cellular orthobiologics

MSCs are undifferentiated multipotent cells capable of differentiating into a limited number of mesodermal cell types, primarily bone, cartilage and fat [40]. They do not possess the broad differentiation potential of totipotent or pluripotent cells. MSCs are most commonly isolated from adipose tissue (AT), bone marrow, umbilical cord (Wharton's jelly), epidermis, dental pulp, and the placenta [40]. They are first expanded and, if required, differentiated *in vitro,* prior to topical application, infusion, or injection [41]. MSCs can also be seeded onto/into bio-scaffolds followed by surgical placement at the injury site [41].

MSCs are immunomodulatory and may downregulate the immune response and inflammation that occur following injury [41]. MSCs secrete anti-inflammatory molecules and through cell-cell interactions, suppress or modulate cellular activation and function, thereby preventing further immune cell infiltration [42]. In addition, neither human nor equine MSCs elicit an immune response. Human MSCs lack human leukocyte antigen (HLA) II expression & have low levels of HLA-I, which contributes to their ability to evade the recipient immune response when utilised in allogeneic transplantation [43]. Equine leukocyte antigen (ELA) is largely analogous to HLA, and equine MSCs likewise express low ELA-I and ELA-II [3]. HLA and ELA expression is heterogeneous among MSC populations; thus, MSC immunophenotype can be influenced by cytokine priming as well as donor-specific factors such as age, breed, and genetic background [44]. Many cytokines, GFs and other proteins found in blood-derived orthobiologics, are also secreted by MSCs. Adipose-derived stromal cells (ASCs) for example produce hepatocyte growth factor (HGF), TGF-β1, VEGF, IL-1RA/IRAP, interleukin 6 (IL-6), interleukin 10 (IL-10) and stromal cell-derived factor 1 (SDF-1) [42].

MSC quality is also highly dependent on the tissue of origin and the age of the donor [42]. Human MSCs from younger donors have greater functional longevity, greater proliferative capacity, improved differentiation potential, and reduced immunogenicity [45]. Burk et al. [46] found that the number of equine MSCs isolated from Wharton's jelly, tendon, or AT was 200 times greater than when derived from cord blood or bone marrow. Human MSCs demonstrate similar results with higher MSC yields from AT when compared to other sources. The isolation of ASCs was first described in 2011 by Zuk et al. [40] from AT lipoaspirate post-cosmetic surgery, where AT is viewed as a "by-product". ASCs are isolated from the stromal vascular fraction (SVF) of AT through an enzymatic digestion process, normally using collagenase, with subsequent centrifugal separation, washing and filtration steps [47]. Equine subcutaneous AT (Sc-AT) is most frequently excised from regions near the tail base, lateral to the insertion of the tail, and over the superficial gluteal muscle. ASCs isolated from AT in these areas are easy to access, high in AT content and lack large veins [48]. AT remains the most accessible source of ASCs in both horses and humans, when compared to other sources [48].

Induced pluripotent or multipotent stem cells (iPSCs or iMSCs) may constitute an alternate cell source in regenerative medicine to combat source-specific heterogeneity and differentiation capacity of adult MSCs. iPSCs are generated by reprogramming differentiated adult somatic cells to a pluripotent stem-like state through the introduction of four transcription factors, also referred to as the Yamanaka factors: Kruppel Like Factor-4 (KLf4), Sex determining region Y box-2 (Sox2), Octamer binding transcription factor-4 (Oct4), and c-Myc [49]. These are delivered via non-integrating reprogramming methods that allow for transient expression, which in turn facilitates more effective differentiation of iPSCs for research and potential therapeutic applications [50]. iPSCs have the capability to self-renew and to be differentiated into any embryonic, and eventual adult tissue [49,50]. Prior to the discovery of the properties of the Yamanaka factors in 2006, there was no ethically approved available source of embryonic stem cells, making iPSC invention novel and of great importance [49,50]. iPSC production is however time consuming, complex [50], and relatively "unknown" in the context of equine research and application, when compared to human iPSC technologies [51]. Many companies are investigating the potential use of human iPSCs in allogeneic settings for broader clinical applications and to mitigate the costly nature of autologous MSC production in a growing market. Equine iPSC generation and molecular pathway analysis will aid in the production and differentiation of these cells for use in the veterinary research and therapeutic space [51].

## 3. *In vitro* research

The mechanism of action of specific orthobiologics is being increasingly studied in various disease models [5]. It is essential to understand how a treatment affects cellular gene expression, cell cycle, apoptotic pathways, inflammatory processes and repair both *in vitro* and *in vivo*; and how these factors work synergistically to produce a response in the body [12]. *In vitro* analysis is used to ascertain the composition of a product and its specific mode of action on a particular cell or tissue type [12]; this should be followed by *in vivo* models which assess the safety and efficacy of the potential therapeutic [52]. These results need to be statistically significant and have biologically relevant outcomes to ensure clinical safety, reliability, validity and repeatability under various environmental conditions [52]. For example, research aiming to quantify cytokine and GF content in PRP which is released within tissues, shows significant variability, largely influenced by production method [53]. Additionally, quantifying and studying proteins found in orthobiologics is complex and multifactorial, due in part to cross-reactivity and synergistic interactions between the molecules. In the context of musculoskeletal disease and injury, interactions between endogenous cytokines and GFs plays a key role in driving tissue and cellular repair [53]. These factors regulate the cell cycle, differentiation and inflammatory response (including angiogenesis and fibrosis) and are actively studied in both research and clinical settings.

A common *in vitro* approach involves supplementing cell culture medium with the blood or protein product of interest. MSCs are often the preferred cell type used for these experiments, as they allow direct investigation of how blood-derived products, or therapeutic molecules, influence cell growth (cell cycle dynamics and apoptosis) [54]. Several *in vitro* studies have shown that adding human blood derivatives to growth medium increases the proliferation of human MSCs while maintaining them in an undifferentiated state [55]. Adding PRP to equine suspensory ligament cells *in vitro* increased cell proliferation and

viability while reducing apoptosis [56], similar to effects seen in human cells treated with PRP [57]. The equine ligament cells demonstrated upregulated collagen type 1 (COL1), matrix metalloproteinase-3 (MMP3) and cartilage oligomeric matrix protein (COMP) gene expression when compared to various controls [56]. In human ACL cells, cultured with PRP, Fallough et al. found increased expression of the collagen type 3 (COL3) gene, an important protein in the extracellular matrix of connective tissue [57]. Similarly, Klatte-Schulz et al. [58] observed that tenocytes treated with a commercial PRP product showed higher expression of COL3A1 (a form of immature, less stable type 3 collagen)) and COX1 (a protein involved in aerobic metabolism).

Internationally, human MSCs are defined by criteria from the International Federation for Adipose Tissue Therapeutics and Science (IFATS) and the International Society for Cell & Gene Therapy (ISCT) [55]. These include adherence to plastic within 24-48 hours following isolation; expression of CD73, CD90 and CD105; lack of CD11b, CD14, CD19 and CD45 expression; and the ability of ASCs to differentiate into chondrocytes, osteoblasts and preadipocytes [59]. Additional ASC criteria include viability, high cell counts, genomic stability, proliferation capacity, cryopreservation ability, with further recommendations for cell senescence testing and secretome profiling [59]. In contrast, there are no standardised criteria for equine MSCs in clinical practice, and methods for isolating ASCs from AT continue to be debated [48,60]. Equine ASCs typically express CD29, CD44, and CD90, but not CD34 and CD45 [60,61], which is at variance with human MSC expression characteristics.

## 4. *In vivo* studies and clinical applications

Currently, OA and tendon injuries are treated palliatively with ice, rest, nonsteroidal anti-inflammatory drugs (NSAIDs, ibuprofen and naproxen), and sometimes hyaluronic acid or corticosteroid (prednisone) injections granting temporary relief [5,42]. Recovery in these tissues is often delayed due to low metabolic efficiency, restricted blood supply, and a limited pool of cells able to support the healing process [62]. OA and tendinopathies can lead to disability, pain, extended rehabilitation, and financial concerns [5,6,14,63]. Effective treatment should aim to modulate the pro-inflammatory microenvironment and restore tissue function through regenerative medicine [5].

### 4.1. Tendon Injury

Tendons are fibrous connective tissue rich in collagen type I and elastin within a water-proteoglycan matrix which connect muscle to bone [64]. Tendinopathies often result from high-intensity exercise and may lead to chronic disability [64]. Common equine tendinopathies include superficial and deep digital flexor tendon injuries and suspensory ligament desmitis [56], while humans are prone to ACL, rotator cuff and Achilles tendinopathies [65].

Tendons are poorly vascularized structures often requiring surgery or prolonged recovery after injury [15,42]. MSCs promote tissue healing by secreting cytokines and GFs, that stimulate neighbouring cells through paracrine signalling [66,67]. Comparably, PRP therapy exposes tenocytes to GFs and anti-inflammatory proteins, promoting matrix production and repair [68]. A2M directly modulates inflammation by binding and neutralizing pro-inflammatory cytokines such as TNF-α and interleukins [22]. It additionally supports angiogenesis, cellular proliferation, and matrix repair through interactions with TGF-β and VEGF — functions indirectly shared by IRAP [22]. A2M can directly sequester TGF-β, limiting fibrotic signalling [69], while IRAP indirectly modulates downstream effects of TGF-β and VEGF via IL-1β inhibition [70]. A2M can also bind VEGF, regulating its bioavailability and local angiogenic activity [69]. A2M plays a dual role in inflammation regulation and tissue repair, making it a promising treatment for OA and soft tissue injuries [71]. It is used as an autologous blood-derived injectable therapy in humans and horses [25]; however, few validated equine quantitative A2M assays exist, limiting clinical monitoring in veterinary practice [72].

Various studies on orthobiologic use in tendinopathies have demonstrated decreased fibrotic tissue formation and restoration of normal tissue function [73]. In horses, injection of bone marrow-derived MSCs reduced reinjury rates by ~38% and improved tissue architecture when compared to non-orthobiologic treatments [74]. Geburek et al. [73] reported that 80% of performance horses with superficial digital flexor tendon (SDFT) injury treated with intralesional PRP recovered to their previous or higher performance level within a year, versus only 50% in controls. Similarly, a chronic SDFT case unresponsive to NSAIDs showed full recovery and tendon fibre realignment one year after repeated injection of autologous PRP and ASCs [74]. Human studies using PRP show improved return-to-sport outcomes, with larger cohorts reporting more than a twofold increase in success rates compared to controls [75]. However, an umbrella review by Cruciani et al. [76] cautions that many PRP studies suffer from methodological imprecisions, inconsistency and high bias risk.

### 4.2. Osteoarthritis (OA)

OA is one of the most common and debilitating musculoskeletal disorders globally in both horses and humans, and is characterized by degeneration of cartilage, bone, ligaments and synovium [77]. Equine and human articular cartilage are similar in terms of location within the joint, cellular composition and biomechanical function, supporting the use of horses as valuable translational models for OA research [78]. Factors such as localized trauma, weight-bearing, genetic predisposition and age affect disease progression [79–81]. As a result, treatments should be tailored to the specific disease process and tissue type affected.

Many human clinical trials are exploring MSC therapies for OA, focusing largely on autologous MSCs for cartilage and bone regeneration through direct injection, scaffolds, or combinations such as MSCs with PRP [42,81]. These trials largely focus on knee OA [82], which is analogous to equine stifle joint OA – predominantly of the femorotibial compartments, lesions involving articular cartilage degeneration and subchondral bone changes including microfractures [83,84]. Other studies have investigated the effect of orthobiologics on carpal [85], fetlock (metacarpophalangeal/ metatarsophalangeal) and hock (tarsal) joints [86], which are comparable to wrist, knuckle and ankle joints, respectively, in humans.

IRAP has been used predominantly in horses with limited use in humans (the latter in the form of ACS). IRAP acts locally at the injury site. Anti-inflammatory mediators, including TGF-β and interleukin-10 are recruited as a consequence of its activity, which together help balance inflammation and support cartilage repair by promoting collagen and proteoglycan synthesis [87]. IRAP indirectly, and A2M directly, neutralize proteases such as MMPs—which are implicated in cartilage erosion in OA [22,37,71]. Several equine orthobiologic devices such as the Arthrex ACP® Double Syringe System (PRP), Pro-stride® Autologous Protein Solution (APS) device (PRP and IRAP), and Alpha2EQ® (A2M) are used for treating equine OA. Processing of these orthobiologics involves the use of the respective medical devices, with a centrifugation step [88]. This is also true for Orthokine® (also known as Regenokine) and other human specific blood processing systems. Autologous patented human ACS (Orthokine® device product) is a globally used experimental therapy for the treatment of OA [89]. The Orthokine® device is only authorized for veterinary use by the United States of America Food and Drug Administration (FDA). However, it has European Medicines Agency (EMA) and Australian approval for both human and veterinary clinical purposes [89]. Irrespective of regulatory approval and authorization, the manufacturers and various published studies claim patients demonstrate improvement in clinical parameters and reduced joint degeneration and inflammation [89].

## 5. Challenges and future perspectives

Translational research involving horses is limited by high maintenance costs, long gestation (11 months), and single births. The accepted roles of horses as companion and working animals raises ethical, socioeconomic and emotional concerns around their use as models of disease and injury [90]. Despite these concerns, the physiological and clinical relevance of equine models remains significant. Both the FDA and EMA recognise horses as valuable preclinical models for orthopaedic research [14,91]. Unlike many companion or livestock species, horses have lifespans of up to 40 years and exhibit aging processes similar to humans in terms of immune function, muscle mass, bone density, and joint health [14]. These parallels support longitudinal musculoskeletal and orthopaedic studies, enhancing the potential translational outcomes of research for both species.

Although the literature on non-cellular orthobiologics is extensive, covering both animal and human studies, it lacks consistently validated or reproducible protocols that can be applied in clinical practice [30]. Variability in production methods results in therapeutics with poorly defined composition and inconsistent quality control, contributing to regulatory ambiguity and potential oversight [92]. Numerous small, randomised control *in vivo* studies examining the effects of non-cellular orthobiologics, suffer from methodological flaws, but still report improved healing [73,92,93]. Additional challenges include short follow-up periods, poor outcome measurements, absence of true placebo controls, patient heterogeneity and commercial bias risk [93,94]. These issues contribute to inconsistent clinical outcomes and scepticism about therapeutic reliability, highlighting the urgent need for standardised protocols and rigorous validation prior to clinical translation.

Lengthy production times, high cost, complexity of isolation processes, protein pathway activation, and purification contribute to the many challenges encountered in producing industrially pure recombinant A2M and IRAP [95]. Various methods have been investigated to improve process efficiency [95]. In clinical settings, large-scale protein production is often not feasible for autologous therapies, thus blood-derivatives are produced that concentrate IRAP or A2M for therapeutic use. These blood-derivatives are essentially modified versions of plasma, which manufacturers claim contain higher levels of A2M and IRAP. Many products remain unverified for composition and are generally considered plasma variants, rather than pure A2M and IRAP [88]. Factors such as centrifugation speed (including acceleration/deceleration speeds), anticoagulant choice (e.g. acid citrate dextrose), temperature, donor variables (age, gender and health status) and activators like calcium chloride influence GF and bioactive molecule levels [92]. Optimising blood-derived, non-cellular orthobiologics involves identifying and characterising the biologically active molecules released during platelet activation and α-granule degranulation.

Blood-derived orthobiologics produced from devices like Restigen®, Alpha2EQ®, Arthrex ACP® and Pro-stride®, have yielded conflicting results regarding GF and cytokine presence and concentrations (A2M, TGF-β1, IL-1β, IL-4, IL-6, IL-10, IL-17a). Ortved et al. [88] found no significant differences in A2M concentrations among three of these devices despite claims the Alpha2EQ® device product would show higher levels. Conversely, Barot et al. [35] observed significant differences in IRAP, A2M and TGF-β1, with the APS system achieving the most consistent and highest concentrations. These varied outcomes suggest that it might be possible to integrate technologies from different veterinary devices to enhance autologous orthobiologic production, with possible extrapolation to humans. Furthermore, individual variability in terms of biological response likely contributed significantly to the differences observed within and between the respective studies.

Poor scientific communication, misinformation and slow regulatory support have created a skewed public perception of MSC therapies and research [96]. The FDA highlights major hurdles for human MSCs including late-phase clinical trial failures and lack of standardized processing and clinical application [97]. Similarly, no FDA approved equine MSC therapies currently exist. Debates persist over autologous versus allogeneic MSC sources and concerns have been raised about safety and efficacy [98]. In Europe, Boehringer Ingelheim has produced Arti-Cell® FORTE, the world's first licenced and authorized equine allogeneic blood-derived stem cell lameness treatment [99]. It has received approval from the EMA veterinary committee (CVMP) and the European Commission [99]. The growing interest and acceptance of MSC use in musculoskeletal diseases has been revealed by ongoing clinical trials, and is supported by extensive research augmented by artificial intelligence (AI) tools. When combined with PRP and other blood derivatives, cell-based orthobiologics may achieve greater therapeutic effects than stand-alone treatments [98]. This evolving landscape suggests a promising future for integrative regenerative therapies, especially using animal models like horses to advance translational research.

## 6. Conclusions

Horses are potentially useful translational models for advancing regenerative therapies in musculoskeletal medicine in humans due to their anatomical, biomechanical, and aging parallels. The "One Health" initiative promotes comparative, collaborative research that deepens understanding of disease and treatment across species, with the potential to benefit both veterinary and human medicine. Cellular products like MSCs and orthobiologics including autologous blood derivatives such as PRP, IRAP and A2M, offer targeted, immune-compatible therapies that address inflammation, tissue degeneration, and healing deficits in OA and tendon injuries. Challenges remain in standardizing production and characterization, especially for equine MSCs, with efficacy impacted by donor variability and device differences. Regulatory hurdles and public perception have also slowed adoption of stem cell therapies, highlighting the need for a detailed description of product composition, mode of action and rigorous clinical trials demonstrating safety and efficacy. Nonetheless, increasing evidence supports the safety and effectiveness of single and combined therapies involving MSCs and orthobiologics. Ongoing research on optimization of cell sources, protein isolation, and product standardization will improve reproducibility and clinical translation. Given the chronic nature and high reinjury rates of musculoskeletal conditions, regenerative therapies informed by equine-human models have the promise to transform care with more effective, durable and minimally invasive interventions. The integration of veterinary and human research, alongside technological innovation, is set to accelerate the development of next-generation regenerative therapies, fulfilling the goals of the "One Health" concept for musculoskeletal disease in both species.

## Declaration of generative AI in scientific writing

AI tools (ChatGPT, OpenAI) were used to assist with text rephrasing and formatting. No AI tools were used to generate original scientific content, analyses, or interpretations. The authors take full responsibility for the accuracy and integrity of the manuscript.

## Ethics in publishing statement

The authors confirm that this review manuscript is original, has not been published previously, and is not under consideration for publication elsewhere. All authors have contributed to the preparation of the manuscript as disclosed in the CRediT section of the manuscript, and have approved the final version for submission to the *Journal of Equine Veterinary Science*.

This manuscript does not involve new experiments on humans or animals and relies solely on previously published literature, which has been appropriately cited. No confidential or non-public data are included.

All potential conflicts of interest have been transparently disclosed, and all funding sources have been fully acknowledged. The authors

affirm that the manuscript complies with the ethical publishing standards and policies of Elsevier and the *Journal of Equine Veterinary Science*.

## CRediT authorship contribution statement

**L.M. Bosman:** Writing – review & editing, Writing – original draft, Validation, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **M.G. Logan:** Writing – review & editing, Writing – original draft, Validation, Funding acquisition, Conceptualization. **A. Miszewski:** Writing – review & editing, Validation, Funding acquisition, Conceptualization. **M.S. Pepper:** Writing – review & editing, Validation, Supervision, Funding acquisition, Conceptualization.

## Declaration of competing interest

M.G. Logan, A. Miszewski and M.S. Pepper are employees and/or shareholders of Altera Biosciences, which operates in the field of universal donor cell technology. These relationships are disclosed to ensure transparency but do not constitute competing interests, neither at present nor for the foreseeable future.

A. Miszewski is the founder and CEO of Novita Biotechnology (Pty) Ltd, which operates in the field of orthobiologics. This relationship is disclosed as a potential competing interest.

L.M. Bosman has no conflicts of interest to declare.

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