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Stem Cells and Animal Health: A New Era of Regenerative Medicine

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Abstract

Regenerative medicine has shifted the central question in veterinary practice from how a disease can be controlled to whether the damaged tissue itself can be rebuilt. This article summarises what controlled trials, cohort studies and meta-analyses in dogs, horses and dairy cattle currently show, reports the published figures alongside their limitations, and outlines what must still be settled before cell-based products can be recommended as routine therapy.

Keywords: regenerative medicine, mesenchymal stromal cells, osteoarthritis, tendinopathy, extracellular vesicles, bovine mastitis

Introduction

Veterinary practice has long been organised around control. Infection is controlled with antimicrobials, pain with analgesics, inflammation with anti-inflammatory drugs, and instability with surgery. These approaches work and will continue to matter. What they generally do not do is restore the original architecture of a tissue once it has been lost. Cartilage that has thinned does not thicken again because a dog is placed on daily medication, and a torn tendon heals with scar rather than with the tightly aligned collagen bundles it started with. Regenerative medicine sets out to close that gap by influencing the biology of repair itself. Enough field data has now accumulated to ask a fairer question than the one usually asked in promotional material: do treated animals do measurably better than untreated ones, and by how much?

How These Cells Actually Work

A stem cell renews itself and gives rise to more specialised cell types. In veterinary work, mesenchymal stromal cells (MSCs) dominate. They can be recovered from bone marrow, adipose tissue, peripheral blood, umbilical cord and even milk, they expand readily in culture, and their low immunogenicity has allowed donor cells to be used across individuals and, in some studies, across species.

The mechanism is not what most owners assume. Labelled cells injected into damaged equine superficial digital flexor tendon showed under five per cent survival at ten days, with numbers falling further, and the survivors stayed at the injection site rather than

migrating to other lesions [1]. Cells that vanish within days cannot rebuild a tendon by becoming tendon. The working explanation is paracrine: MSCs release growth factors, cytokines and extracellular vesicles that alter the behaviour of host cells already present, dampening inflammation, encouraging vessel formation and shifting matrix turnover [2, 3]. They behave less like spare parts and more like short-term biological instructions.

Table 1. Mesenchymal stromal cell sources used in veterinary practice and their trade-offs.

Source	Main species	Advantage	Limitation
Bone marrow	Horse, dog	Strongest clinical outcome data in equine tendinopathy [4, 5]	Invasive harvest; three to four week culture delay
Adipose tissue	Dog, horse, cattle	Large yield from a small surgical sample [6, 7]	Weaker racehorse outcomes than bone marrow [5]
Peripheral blood	Horse, dog	Minimally invasive; suits allogeneic banking [8, 9]	Lower initial cell numbers
Umbilical cord, fetal adnexa	Dog	Off the shelf; no donor procedure [10, 11]	Regulatory position on xenogeneic use varies
Milk-derived mammary cells	Cattle	Collected non-invasively at milking [12]	Early stage; characterisation evolving

The Evidence in Dogs

Canine osteoarthritis is the commonest target. In a multicentre, double-blinded, randomised, placebo-controlled trial of 80 client-owned dogs with naturally occurring elbow or hip osteoarthritis, a single intra-articular injection of equine umbilical cord MSCs gave its best result at eight weeks, when 63 per cent of treated dogs improved on force plate gait analysis, 77 per cent improved on orthopaedic examination and 65 per cent of owners judged quality of life to be better. At eighteen months, 59 per cent of owners reported benefit lasting beyond six months, with no systemic or permanent adverse events [10]. Smaller studies agree in direction: 25 dogs given autologous adipose MSCs with platelet-rich plasma showed significantly lower Liverpool Osteoarthritis in Dogs scores by week four and sustained staging and symmetry gains through six months [6], and a retrospective series of 245 referral dogs found a mean interval of 451 days before repeat treatment was needed [7]. Dose is not linear. In a controlled canine model, intravenous xenogeneic peripheral blood MSCs worked best at 0.3 million cells rather than at higher doses [8].

The Evidence in Horses

Equine tendinopathy has the longest follow-up in the field. In a multicentre, blinded, placebo-controlled trial, 100 horses with natural superficial digital flexor tendon or suspensory ligament injuries received tenogenically primed allogeneic MSCs (66) or saline (34). By day 112, fibre alignment improved in 100 per cent of treated horses against 54.5 per cent of controls, echogenicity in 97.0 against 57.6 per cent, and lesion cross-sectional area fell by 27.6 mm^2 against 4.6 mm^2 (all $p < 0.001$) [9]. A retrospective cohort of 213 Thoroughbreds on an identical twelve-month exercise programme offers the most sober comparison: bone marrow MSCs were associated with roughly threefold higher odds of returning to racing (OR 3.19; 95% CI 1.55 to 6.81), while allogeneic adipose-derived cells showed no significant association with any outcome [5]. Cell source is not a detail.

Table 2. Reported reinjury rates after cell-based treatment of equine tendon and ligament injury.

Study design	Horses (n)	Reinjury after cell therapy	Comparator
Cohort, autologous BM-MSC [4]	168	18% of those returning to full work	56% (historical conventional)
Cohort, autologous BM-MSC [13]	141 (113 followed)	27.4% overall; 25.7% National Hunt	Published non-cell treatments
Cohort, allogeneic AT-MSC with PRP [14]	19	10.5% at 24 months	None (single arm)
Cohort with pooled meta-analysis [3]	104 lesions	18% at 24 months (95% CI 0.11-0.25)	44% conventional (0.37-0.51), p < 0.0001
Randomised, placebo-controlled [9]	100	12 of 53 treated horses reinjured	24 of 26 saline-treated reinjured

These figures carry a caveat the field itself supplied. A PRISMA-compliant review screened 764 studies, included 21 and carried 17 into meta-analysis. MSCs, alone or with platelet-rich plasma, reduced reinjury risk, but there was no increase in the likelihood of returning to performance, and most included studies showed poor quality and high risk of bias [15]. The honest summary is that cell therapy appears to protect the repaired tendon rather than guarantee a return to the racetrack.

Regenerative Medicine Enters the Dairy Barn

The economic case may eventually be strongest in livestock. Antibiotics, whatever their bacteriological effect, do not regenerate lost secretory tissue and carry withdrawal periods and resistance concerns. Dairy cows with induced Staphylococcus aureus clinical mastitis received two intramammary doses of 25 million bovine fetal adipose MSCs; treated quarters had significantly lower colony forming units in milk than untreated quarters, and repeat dosing in healthy heifers produced no clinical or haematological change [16]. A field study in 39 Polish Holstein-Friesian cows, 36 cytologically mastitic, found falling total bacterial counts, S. aureus, Enterobacteriaceae and somatic cell counts after allogeneic MSC treatment, with the effect achieved by the intramammary or combined intramammary and intravenous route [17]. Cells taken from milk itself are an appealing wrinkle: their secretome increased fibroblast migration, promoted endothelial network formation and inhibited mastitis-associated bacteria including antibiotic-resistant strains in vitro [12]. That antimicrobial property is population-specific, since adult bovine MSC and induced pluripotent stem cell (iPSC) secretomes supported regeneration but showed minimal antibacterial activity [18].

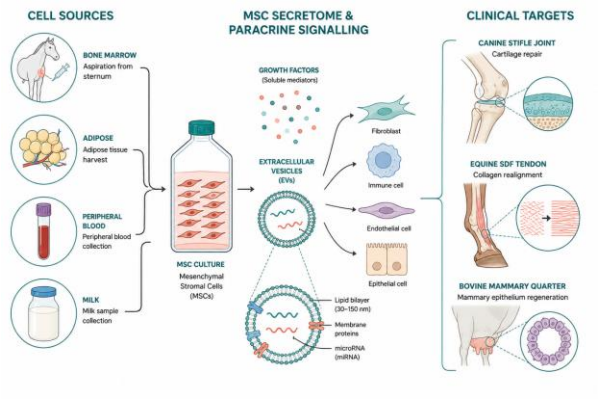

Figure 1. Schematic overview of veterinary regenerative medicine, showing mesenchymal stromal cell sources, the paracrine mode of action through growth factors and extracellular vesicles, and the principal clinical targets in dogs, horses and dairy cattle.

When the Cells Themselves Are Not Needed

If most of the benefit is paracrine, the living cell starts to look optional. MSCs release extracellular vesicles, including exosomes of roughly 30 to 150 nanometres, carrying proteins, lipids, messenger RNA and regulatory microRNAs into recipient cells [2, 19]. In preclinical wound models, MSC-derived exosomes accelerated closure by 25 to 60 per cent within ten to fourteen days, raised the M2 to M1 macrophage ratio 1.5 to 3.2-fold, increased microvascular density by 30 to 70 per cent and increased collagen deposition 1.4 to 2.0-fold; hydrogel, scaffold or microneedle delivery extended retention at the wound bed two to five times over free vesicles [20]. Much of this work is preclinical and aimed at human medicine, so the numbers indicate direction, not veterinary dosing. The attraction is that a vesicle preparation can be characterised, standardised, frozen and shipped in ways a living cell suspension cannot. The obstacles are scalable isolation, batch consistency and a regulatory pathway that does not yet exist in most countries. Reprogrammed cells sit further back still: bovine iPSCs have been maintained beyond 70 passages with normal karyotype and redirected towards a mammary phenotype in vitro, but tumorigenic potential and manufacturing scale keep them a research platform rather than a treatment.

What the Evidence Does Not Yet Show

Several limitations run through the literature and should be stated plainly to clients. There is no single stem cell product, and the racehorse data show source differences translating into different clinical outcomes [5]. Manufacturing varies between laboratories, so passage number, viability and culture conditions change what is actually injected. Optimal dose is unresolved and is not simply a matter of using more [8]. Long-term safety data remain thin, particularly in food-producing animals where residue questions are unavoidable. Above all, much published work is uncontrolled, and the field's own meta-analyses describe high risk of bias in most studies [15]. None of this argues against the therapy. It argues against overselling it.

Conclusion

Regenerative medicine has earned its place in veterinary practice, but on narrower ground than the surrounding enthusiasm suggests. The strongest case is equine tendon and ligament injury, where randomised and cohort data converge on reduced reinjury risk, and canine osteoarthritis, where placebo-controlled work shows real if time-limited functional gain. The most interesting frontier may be the dairy shed, where cell-based and cell-free approaches offer something, antibiotics cannot, namely tissue restoration without a withdrawal period. What the field needs now is standardisation: agreed cell characterisation, defined potency assays, adequately powered controlled trials and long-term follow-up. Instead of only treating damaged tissue, can we help the animal rebuild it? For a growing but still specific list of conditions, the answer is a qualified yes.

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