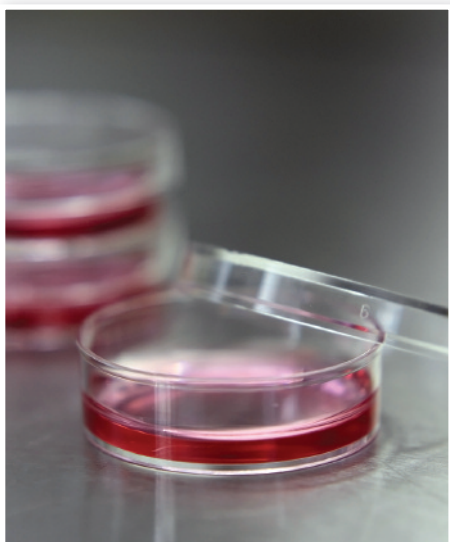


# Stem Cells: New Therapy for Old Diseases

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The public misconception of stem cells as a panacea persists, but stem cell therapy could become another tool for veterinarians to treat the pain and inflammation associated with osteoarthritis and tendon and ligament injuries.

Refinements have been reported in the processing of fresh adipose stem cells and expansion of stem cells (from either bone marrow or adipose) through culture.

## Background

Stem cell applications can pertain to veterinary medicine in two ways:

- *Tissue engineering* involves ex vivo growth of functional tissues and organs as well as delivery of functionalized engineered materials in combination with growth factors or cells.
- *Cell therapy* involves the introduction of undifferentiated stem cells to treat specific diseases or conditions.

Recent literature has shown strong evidence that stem cells work by homing to the injury site and producing cytokines and growth factors.<sup>1,2</sup> These paracrine actions have been noted to produce the following effects<sup>1,2</sup>:

- Decrease in inflammatory mediators and clinical inflammation
- Stimulation of local progenitors to replace damaged tissue
- Blocking or remodeling of scar tissue
- Stimulation of blood vessel formation (angiogenesis)
- Modulation of the immune response by direct effect on immune cells (eg, T lymphocytes, regulatory T cells, natural killer cells, B lymphocytes)

COMP = cartilage oligomeric matrix protein, MSCs = mesenchymal stem cells

## Indications



Initial forays into veterinary stem cell therapy began in 1995 with injections of unprocessed bone marrow into equine suspensory ligaments.<sup>3</sup> Refinements have since been reported in the processing of fresh adipose stem cells and expansion of stem cells (from either bone marrow or adipose) through culture.<sup>4,5</sup>

To date, clinical use of mesenchymal stem cells (MSCs) in veterinary medicine has been limited and is still in development. Initial data suggest that the main mechanism of action of MSCs is the differentiation of transplanted cells to replace damaged host tissue.

The strongest evidence for use of regenerative stem cells in veterinary medicine is in the areas of tendon and ligament repair and treatment of chronic osteoarthritis.<sup>4,6-8</sup> In addition, this therapy has shown promise for renal disease, dermatologic conditions, and muscle tear repair.<sup>9,10-12</sup>

## Case Studies



Two blinded, prospective studies involving equine tendonitis have been conducted using the same experimentally induced lesion model. The first study used a fresh population of adipose-derived stem cells and the second used cultured bone marrow; both studies relied on central processing for standardization.<sup>6,7</sup>

The adipose study showed statistically significant histologic and biochemical improvement (type III collagen and cartilage oligomeric matrix protein [COMP]).<sup>6</sup> In the bone marrow study, no individual histologic parameters differed significantly between treated and control tendons<sup>7</sup>; COMP expression in control tendons was greater than COMP expression in tendons treated with bone marrow MSCs. In this horse tendon model, adipose had stronger evidence of improved healing.

To study stem cell therapy in canine patients with naturally occurring osteoarthritis, a randomized, blinded, placebo-controlled study was conducted at multiple specialty hospitals.<sup>8</sup> The study demonstrated statistically significant clinical improvement in the adipose-derived stem cell group for all posttreatment evaluation times when compared with a control group treated with saline.

Measured parameters included lameness at walk and trot, pain on manipulation, and range of motion.<sup>8</sup> Although this study was small, it was the first blinded, placebo-controlled clinical trial in dogs that illustrated the benefits of injecting stem cells directly into arthritic joints.<sup>9,10</sup>

It is important to choose a stem cell processing provider carefully. Without the proper equipment, patients may not be given correct doses<sup>12</sup>; little has been published on proper dose schedules.

Two recent studies illustrated some mechanisms that make stem cells an intriguing addition to pain management. In the first study, stem cells were shown to block pain both peripherally and centrally at the opioid receptor.<sup>13</sup> The second study showed how MSCs can produce a powerful natural lubricating molecule called *lubricin*.<sup>14</sup> New data are regularly released on the potential uses of stem cells.

## Contraindications

In patients with severe instability (eg, acute ligament rupture, spinal injury), stem cell therapy is not recommended in place of surgery. Although the documented clinical risk appears low, the conservative approach is to limit stem cell therapy to patients without active neoplasia until further studies can be conducted to document its safety.<sup>15,16</sup>

Additional contraindications are not currently known.

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## A Quick Comparison

**Adipose** collection has less morbidity and significantly higher yields of stem cells than bone marrow collection, which precludes the need for expansion by tissue culture.<sup>17,18</sup>

**Bone marrow-derived** stem cells have been more commonly studied, but there is a delay in treatment because of the necessity for cellular expansion.<sup>19</sup> This delay may promote scar tissue formation or further damage injured tissues.

The ideal source of stem cells for various indications is likely variable and will require more investigation. In either case, there are virtually no reported adverse effects in the peer-reviewed literature when unadulterated adult stem cells are used in vivo.

## Advantages

A multimodal approach involving NSAIDs and other therapies has had widespread acceptance in managing the debilitating effects of arthritis. Stem and regenerative cells are being studied to see how cell-mediated benefits can add to this approach. This therapy may become part of the multimodal approach.

Most nonsurgical therapies for orthopedic conditions (ie, weight loss, exercise, supportive devices, pain medications, supplements, corticosteroids) can provide short-term symptomatic relief for arthritis. Stem cells have the potential to address the actual underlying disease process through tissue regeneration rather than daily or monthly lifelong treatment.<sup>20-22</sup>

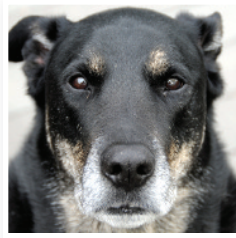
The reintroduction of an animal's own stem cells to a micro-environment (eg, joint, tendon) may signal other cells to facilitate repair via their antiinflammatory, angiogenic, antiapoptotic, antiscarring, immune-modulating, and tissue-regenerating abilities.<sup>2</sup> However, although MSCs may positively influence the environment, questions of how they do it, how they are controlled, and whether correct factors are being produced are not well understood.

## Disadvantages



Tissue collection for administration of stem cells typically requires general anesthesia in small animals. Joints may be painful for a few days postinjection. Injection into arthritic joints necessitates skill and practice, and some general practitioners prefer to refer cases for intraarticular injections.

## Economic Impact



A young patient diagnosed with osteoarthritis may require surgical intervention, rehabilitative therapy, and potential lifelong prescription for pain medication. Stem cells may have a high up-front cost, but the cells can be stored for the lifetime of the animal and retreatments—if necessary—

cost less than the initial process. Whether cells can be effective after being stored over time is not yet known.

## Conclusion

Many veterinarians and owners have considered stem cell therapy as a last resort, and patients that may not have been candidates for treatment with NSAIDs have benefited from autologous-derived stem cell therapy.

As the body of science in veterinary stem cell therapy increases, veterinarians may start collecting stem cells prophylactically at spay and neuter, storing the cells for later indications and uses.

During the past 10 years, autologous adult stem cells have been shown to be safe (and have become a standard of practice in equine medicine). Most small animal pet insurance companies accept use of stem cells in treatment of different conditions, as long as the disease itself is covered by the policy.

We are witnessing the early stages of an effective new therapy. Future science will likely prove that stem and regenerative cell therapies should be part of multimodal approaches to increase chances for the best outcome for many veterinary patients. Stem

## Seeking the Science Behind the Anecdote

Overt success of regenerative medicine in humans (notable examples include bone marrow transplantation and skin and corneal regeneration) is based on a robust preclinical rationale and sound scientific evidence of efficacy in preclinical models. Application of regenerative medicine is growing rapidly, and it may replace or influence many current treatments in the future.

In veterinary medicine, meanwhile, use of unproven stem cell therapies is widespread. Anecdotes of successful out-

comes after stem cell therapy in horses, dogs, and cats abound, yet scientific evidence for its efficacy in veterinary medicine is lacking. Stem cells have already shaped contemporary medicine of humans, and they may do the same in veterinary medicine, but only if they are properly evaluated in the laboratory setting and translated to the clinical setting based on results of rigorous trials.

Until science catches up with the resourceful marketing and overt optimism associated with stem cell therapy in veterinary

medicine, owners are encouraged to have their veterinarians look at the available scientific evidence before making a decision to pursue stem cell therapy. Equally important is that veterinarians should not be persuaded by “miracle” success stories or marketing techniques that tout the benefits of stem cell therapy in the clinic. Anecdote cannot be a substitute for scientific evidence.

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cell therapy will only become more refined and sophisticated—and potentially more affordable. ■ **cb**

See Aids & Resources, back page, for references & suggested reading.

### What's Next?

Veterinarians need to investigate commercial stem cell laboratories and ensure that they are acquiring services from an ethical company with a good quality assurance program.

Who is actively conducting clinical research for stem cell therapies in both human and veterinary patients is a commonly asked question. Examples of some established programs include:

**University of California, Davis Stem Cell Program**  
ucdmc.ucdavis.edu/  
stemcellresearch

**Indiana University Vascular & Cardiac Center for Adult Stem Cell Therapy**  
stemcellsignature.iupui.edu

**University of Minnesota Stem Cell Institute**  
stemcell.umn.edu

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MSCs = mesenchymal stem cells