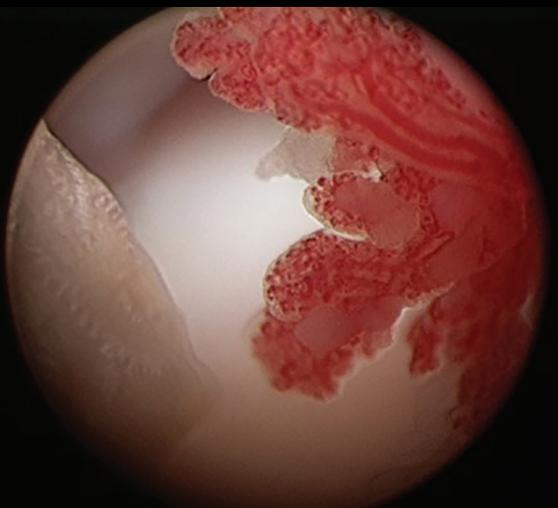


Steven M. Fox, MS, DVM, MBA, PhD
John M. Donecker, VMD, MS



▲ **FIGURE 1** Arthroscopic view of synovitis, characterized by infiltration of the synovial membrane with inflammatory cells resulting in angiogenesis and hyperplasia of the synovium

KEY POINTS

- ▶ Synovitis likely plays a pivotal role in the pathogenesis of OA, and a multimodal approach to managing OA may provide the best outcomes.
- ▶ Synovetin OA is a groundbreaking new treatment that provides durable relief from the chronic pain and inflammation of canine elbow OA. With 1 fast intra-articular injection, effects last up to 1 year, providing veterinarians and pet owners with a convenient approach to managing chronic pain and inflammation.

EXUBRION
THERAPEUTICS

Synovetin OA

Breaking the Vicious Cycle of Inflammation in Canine Osteoarthritis

Osteoarthritis (OA) affects ≈20% of adult dogs¹ and is increasingly understood to be a vicious cycle. Recognizing this can open up new methods of treating this complex condition.¹

OA has traditionally been viewed as a cartilage-only disease; however, synovitis (ie, inflammation of the synovium) is a common clinical finding.² Clinical signs of inflammation, histologic inflammation in osteoarthritic synovial tissue, and early cartilage lesions at the border of the inflamed synovium strongly indicate that synovitis plays a pivotal factor in the pathogenesis of OA.³

Synovial inflammation is implicated in many signs of OA, including joint swelling and effusion. The OA synovium has both inflammatory and destructive responses that depend largely on macrophages. These effects are cytokine-driven primarily through a combination of interleukin-1 and tumor-necrosis factor α .⁴ Such observations are stimulating increased investigation into dynamic changes within the microenvironment of the synovial joint. The goal of this research is to develop therapies that can decrease both inflammatory synovitis and the production of degradative enzymes, which contribute significantly to the progression of OA.⁴ With this goal in mind, a new focus for chronic pain management is the macrophage, which acts as the conductor of the inflammatory orchestra.

Inflammation, pain, impaired mobility and function, and structural changes characterize OA and contribute to its progression.⁵⁻⁷ Pain is the hallmark of OA and results in both local and distant deterioration of the musculoskeletal system as a result of decreased and altered mobility. The pathologic process of OA, including joint capsule thickening and periosteal reactions, causes an altered range of motion, compounding musculoskeletal changes. Continual nociceptive input in the CNS results in somatosensory system deterioration and central sensitization with wind-up, amplifying the perception of pain.⁸ Presently, the functional and structural changes associated with canine OA are incurable.

Early intervention has the greatest potential for providing the most effective management of OA by providing the opportunity to initiate an appropriate long-term care plan and to disrupt the progressive, vicious cycle of multidimensional deterioration involving both the neurologic and musculoskeletal systems.⁹ From

such recognition has come a proposed instrument for staging canine OA, the Canine OsteoArthritis Staging Tool.⁹ This tool can help identify OA at an early stage, noting preradiographic changes and improving dog owners' awareness of early-stage OA. Such clinician/pet owner synergism can help drive earlier and, therefore, more successful treatment by slowing disease progression.

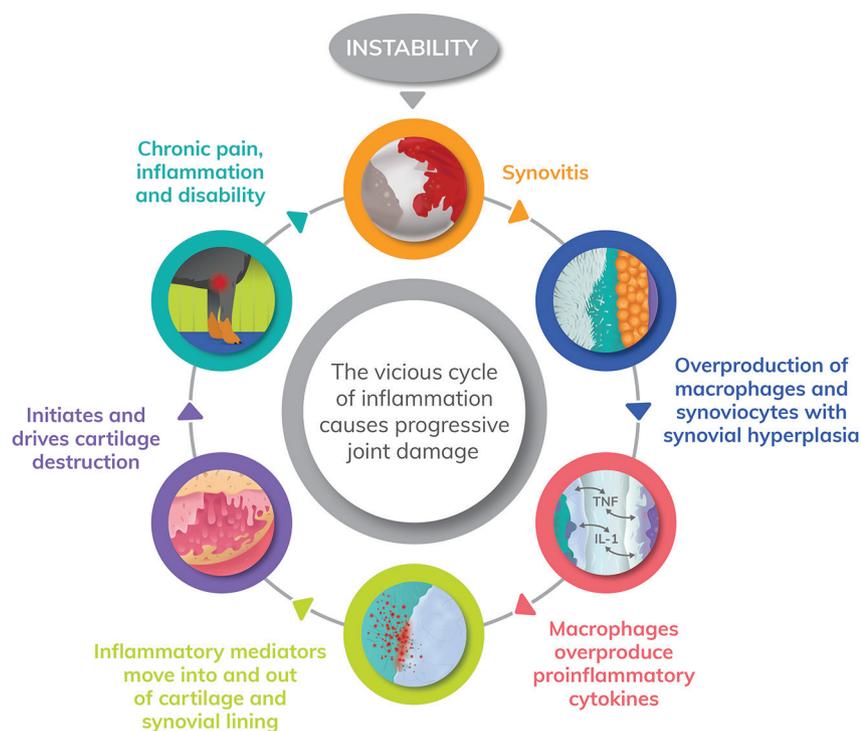
Synovetin OA[®] is a groundbreaking new treatment that provides durable relief

from the chronic pain and inflammation of canine elbow OA. With 1 fast intra-articular injection, effects last up to 1 full year, providing veterinarians and pet owners with a convenient approach to managing chronic pain and inflammation. By depleting proinflammatory macrophages (the source of chronic pain), Synovetin OA breaks the vicious cycle of inflammation, providing effective, long-lasting, safe, nonsystemic relief. During 3 separate year-long clinical trials involving 69 client-owned dogs, Synovetin OA was shown to

be safe and effective.¹⁰ One of these studies also showed Synovetin OA to be safe for re-administration to a previously treated elbow joint.

Radiosynoviorthesis (the restoration of the synovium using a radioisotope) is a well-established human procedure, having been used around the world for >60 years, and is associated with a low adverse event rate ($\approx 0.013\%$).¹¹ Arthritic joints, which contain proinflammatory macrophages recruited during synovial hyperplasia, engulf colloid-embedded tin-117m microparticles, the active agent in Synovetin OA, and transport this complex to areas of synovial inflammation. Thereafter, tin-117m conversion electrons destroy the engorged macrophages responsible for inflammation via the noninflammatory process of apoptosis. This results in the synovium more closely reflecting the preinflammatory state and retards nociceptive transduction (pain). After decay, residual microparticles of inert tin are cleared via the lymphatic system to the liver.

Synovetin OA can be injected as an outpatient procedure. It is available from licensed specialty treatment centers, which can be located at Synovetin.com



▲ **FIGURE 2** The vicious cycle of inflammation. Overview of OA as a process rather than a disease, beginning with synovitis of a synovial joint caused by various sources, including trauma, instability, or idiopathic causes.¹²⁻¹⁸ Regardless of etiology, histologic changes in the synovium include hyperplastic and hypertrophic synoviocyte changes and robust angiogenesis. Synoviocytes are mostly macrophages, and these changes cause an overproduction of proinflammatory cytokines (eg, matrix metalloproteinases, interleukins, tumor-necrosis factor α) that become part of the joint fluid milieu moving to and from synovial and cartilage tissues as the dog loads and unloads the joint. Matrix metalloproteinases, aggrecanases (metalloproteinases which cleave the aggrecan building blocks of cartilage), and nitric oxide, an important mediator in chondrocyte apoptosis, are particularly destructive to cartilage. With cartilage catabolism comes progressive inflammation, pain, and disability, contributing to the vicious cycle.

For references, please visit cliniciansbrief.com/article/breaking-vicious-cycle-inflammation-canine-osteoarthritis

For full prescribing information for Synovetin OA[®], see next page.