

TECHNICAL BULLETIN



The New Science of Osteoarthritis (OA) Pain and Inflammation



THE NEW SCIENCE OF CANINE OA PAIN

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INTRODUCTION

Osteoarthritis continues to be a significant disease for humans and dogs alike. The lack of therapeutics based on new targets to help manage the pain associated with osteoarthritis has been a gap for over 20 years in both the human and veterinary professions. The toll taken on the patient and family has led to increased emphasis on translational medicine, and novel approaches to understanding the molecular and cellular basis of OA and OA-associated pain. New scientific approaches, especially at the “omics” level, have been employed to understand gene expression and subsequent protein changes associated with osteoarthritis as the disease progresses. This scientific approach has broadened our appreciation for the familiar biological processes, such as prostaglandin pathways, and has expanded our knowledge to include new biological processes and mediators demonstrated to impact the disease. The goal of this bulletin is to update veterinarians on our understanding of these emerging signaling pathways in osteoarthritis and how this emerging science may result in new therapies for the veterinary profession.



Osteoarthritis is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness.¹

– working definition from the Osteoarthritis Research International (OARSI)

The New Science of Osteoarthritis (OA) Pain and Inflammation



OA IS AN INCREDIBLY IMPORTANT AND HIGHLY PREVALENT DISEASE IN DOGS

As a progressive and currently incurable disease, early diagnosis and management can help reduce pain, improve mobility and improve a dog's quality of life.

Osteoarthritis is the most common musculoskeletal disease in both humans, which is currently estimated to affect over 240 million people globally, and dogs, where estimates in the late 1990's were ~20% of dogs over the age of one year old being affected.² However newer information suggests that it is almost double that. In a recent study using a canine OA screening checklist, close to 40% of dogs screened had clinical signs of OA.^{3,4}

OA is, in many respects, a quiet epidemic as it is often under-diagnosed.

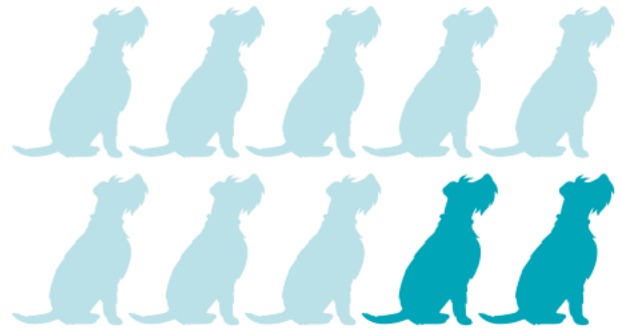
In dogs, the underlying etiology is related to conformational abnormalities of the joint, obesity or joint injury. Because the impact of joint confirmation is such a major driver of disease, the development of OA can begin much earlier in life for dogs than what is often expected.

Another under-evaluated group are small dogs. Although they often have similar joint changes to large-breed dogs, their physical changes may be compensated for by dog owners lifting or carrying them. However, they likely still have pain related to the OA.

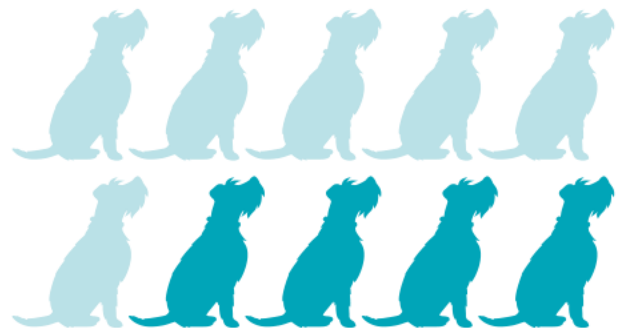
Dogs hide signs of pain and pet owners often overlook signs, attributing them to "old age." This may only lead pet owners to recognize signs very late in the disease when the signs are obvious and dramatic.

Osteoarthritis pain should not simply be viewed as a problem confined to peripheral joints – the pain from OA has a profound widespread effect on individuals who suffer from the disease.

Perception of OA Incidence is ~20%



But, with active screening, may be closer to ~40% of Dogs



"Animals are non-verbal beings. They can't tell us that they hurt in a verbal way. They can only tell us by their behavior, their unwillingness to socialize, their unwillingness to play ball and so forth. If we don't treat that pain of arthritis, we're taking all of that away from them. And that's really sad, because then they're not going to have a fuller life that they really deserve."

– Mike Petty, DVM, CVPP, CVMA, CCRT, CAAPM





BROAD IMPACT OF CHRONIC PAIN

There is now a greater understanding of the negative impact of OA pain, both in humans and dogs. In 2017, the Pain in Animals Workshop (PAW) held at the national Institute of Health (NIH) focused on chronic pain in companion animals associated with osteoarthritis, cancer and neuropathic pain. This meeting brought together leading advocates in the areas of government, academia, industry and pain management to discuss and work on improving our ability to recognize and measure chronic pain – a fundamental prerequisite to being able to treat

OA pain. An important focus of this meeting was to highlight the multiple dimensions impacted by OA pain. In a subsequent publication, the holistic consequences of chronic pain that extend beyond the impact on gait, movement and the ability to perform the activities of daily living were expanded to include affective, cognitive and the human-animal and animal-animal bond relationship.⁵ In addition, the impact on sleep and sensitivity to environmental stimuli were highlighted, along with approaches to measuring the impact of OA pain on all these dimensions.



Adapted from Lascelles BDX et al. Measurement of chronic pain in companion animals: discussions from the Pain in Animals Workshop (PAW) 2017. *The Veterinary Journal*. 2019;250:71-78.





CURRENT TREATMENT OPTIONS AND GAPS

Current treatment options have some limitations. Pharmacological treatment of pain centers around non-steroidal anti-inflammatory drugs (NSAIDs). Globally, several NSAIDs are approved for use in dogs, including the newest NSAID, grapiprant.

NSAIDs are used to relieve pain and thus promote functional improvement.⁶ For many years, patients suffering from OA have benefited from this class of drugs.

Despite their widespread use and clear beneficial therapeutic effects, NSAIDs are not always adequately effective when used as a monotherapy.⁷ Additionally, there are safety and tolerability concerns with their use in some dogs.⁸⁻¹¹ Daily administered medications can have compliance issues, with pet owners not always remembering to administer the medication, and some dogs are just hard to dose orally.¹² Pet owners also may not recognize signs of pain (or are not at home to see the signs) and may elect to skip doses, resulting in intermittent and inconsistent dosing.¹² Lastly, some are labelled for use at lowest-effective dose, which may cause confusion as to what this means in terms of practical administration, leading pet owners to drop to subtherapeutic doses for lack of knowing what signs to monitor.

Beyond NSAIDs, effective pharmacological treatment options for the control of pain are very limited.¹³ Even with orally administered medications, compliance can be an issue with pet owners not always recognizing signs of pain and/or remembering to administer the medication.^{12,14}

A variety of putative analgesic drugs have been used to help control OA pain, mainly as adjunctive drugs in addition to NSAIDs. However, evidence for efficacy of adjunctive analgesics is extremely limited.^{7,15,16} In fact, a 2018 placebo-controlled publication demonstrated that tramadol has no clinical impact on dogs suffering from osteoarthritis of the elbow or stifle.¹⁶ Additionally, there are few proven non-drug therapies, and none that have been shown to provide rapid pain relief.

OA related-pain remains a challenging clinical entity to treat and, indeed, OA-associated pain is one of the most common reasons for euthanasia in dogs.^{17,18}

“OA really can be what I’ve termed ‘a silent killer’ because when it robs patients of their life quality... that loss of well-being is often the motivating concern that will cause a dog owner to begin to consider end-of-life decisions or perhaps pursue euthanasia.”

– Ross H. Palmer, DVM, MS, DACVS

There is an urgent need to develop effective treatments for OA-related pain in dogs and minimize the negative consequences of pain, and the associated suffering.





**There has been no new class of medication
to manage OA pain in over 20 years
in both human and veterinary medicine.**



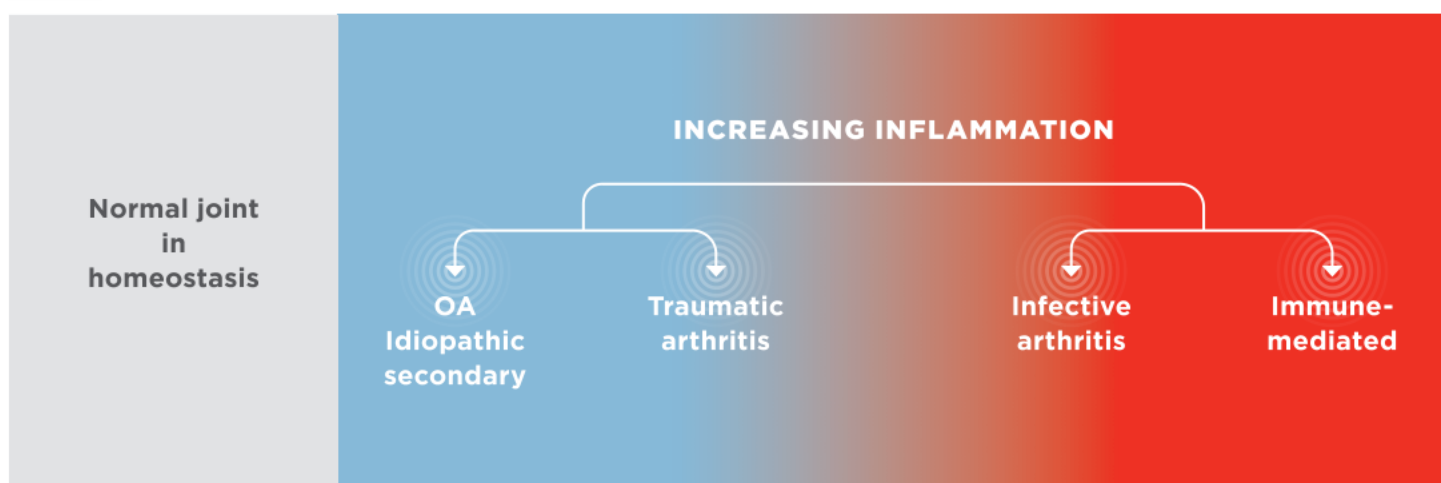


INFLAMMATION

THE NEW SCIENCE OF OA DISEASE

Osteoarthritis (OA) has traditionally been classified as a noninflammatory arthritis. This was based on early work that evaluated synovial fluid, comparing the quantity of inflammatory proteins in various arthritides. Such studies showed that OA fluid had significantly lower amounts of inflammatory proteins than rheumatoid arthritis (RA) or septic arthritis samples^{19,20} (Fig. A).

FIG. A



It is now understood that the degree and characteristics of inflammation vary across the different arthritides. Although largely overshadowed by the more pronounced histologic and biochemical inflammatory abnormalities in RA, studies from as early as 1959 revealed elevated levels of inflammatory plasma proteins in both the blood and synovial fluid of patients with OA²⁰ compared to controls.

More recently, the use of molecular, genomic and proteomic insights has expanded our understanding of the ongoing immune processes in OA.²¹ Such research

has uncovered a new molecule of interest, Nerve Growth Factor (NGF). NGF is elevated in diseased joints,²² it clearly plays a role in pain, and new science is emerging regarding its interactions with cells and tissues in the diseased joint.

The following section highlights new thinking in the science of OA disease: inflammation, including neurogenic inflammation, expanded understanding of the role of joint tissues, and the current understanding of the role of NGF in the osteoarthritic joint.





INFLAMMATION

OA INFLAMMATION IS LOW-GRADE AND CHRONIC

OA is associated with multiple risk factors, most notably conformation, joint trauma and metabolic/obesity. These may be thought of as “inciters” to the disease. Sokolove and Lepus (2013) have postulated that “Given its complex etiology, OA should not be thought of as a single disease, but rather as the clinical endpoint of numerous disorders leading to the eventual failure of one or more joints of the body. Even with different starting points, evidence suggests that the changes characteristic of OA share a common final pathway that operates to perpetuate joint destruction and eventual joint failure.”²¹

Once the joint faces an “inciting factor,” tissue damage occurs triggering the immune system to begin its traditional inflammatory role, including the classic signs attributable to mechanical injury or infection. Acute inflammation persists for a couple of days or weeks and requires the presence of the external stimulus.

As time progresses beyond these initial weeks, the joint cells and tissues undergo transitions that ultimately lead to a state of low-grade, chronic joint inflammation that drives progression toward clinical OA.²³ It is interesting to note that this low-grade chronic inflammation is not what we typically think of when describing inflammation clinically.

In clinical osteoarthritis, the normal remodeling and anti-inflammatory properties within the joint have been overcome and are in a pro-inflammatory, chronic catabolic state.

Unlike RA, OA does not appear to be associated with a robust adaptive immune response. However, activation of the innate immune system is a central feature of both diseases.²¹



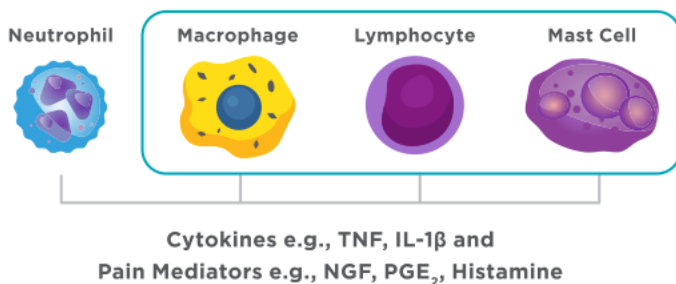


INFLAMMATION

IMMUNE CELLS IN CHRONIC OA INFLAMMATION

The most frequent types of immune cells found in OA are macrophages, T lymphocytes and mast cells (MCs) (Fig. B).²⁴ The involvement of many aspects of the immune response in OA, along with other mechanical and biochemical factors, makes OA a complex disorder.²⁵

FIG. B: IMMUNE CELLS



Whereas the numbers of most immune cells (for example, macrophages and T cells) in synovial tissues are lower in OA than in RA, the number of mast cells in OA is as high as, or sometimes higher than, in RA.²⁶

In this next section, we will discuss current theories and science related to selected cells and tissues associated with the joint, with an emphasis on how NGF affects function and responses of cells and tissues. This is not an all-inclusive examination. As stated at the beginning, this is an area of intense work and new information is coming forward at a rapid pace.

ROLE OF MAST CELLS IN CHRONIC OA

Mast cells are well known as effector cells of the innate immune system and are capable of producing cytokines and growth factors including NGF.^{27,28} Research is emerging that dysregulation of the innate immune system, including mast cells, is likely involved in the pathogenesis of osteoarthritis.²⁹ Different activation stimuli lead mast cells to differentiate and respond in different ways,²⁹ for example, a mast cell associated with allergy is different than a mast cell associated with OA joints. More research is needed to better

understand mast cells' role in OA. At the synovial level, mast cells are located mainly in the synovial membrane and joint capsule, mostly along blood vessels and nerve endings of the joint.²⁸ Synovial mast cells interact with these blood vessels and sensory nerves. Alterations in their regulation can affect their function and physical nature.²⁸ Emerging evidence indicates mast cells help to orchestrate inflammation and neuroinflammation within the joint.^{28,29}

Mast cells are a source of many types of growth factors. In addition to NGF, these also include vascular endothelial growth factor (VEGF) and angiogenin. It is thought that the release of angiogenin could contribute to the development of angiogenesis associated with OA.²⁸ The levels of these growth factors are altered in joints with chronic OA. NGF has been demonstrated to be elevated in the synovium and associated fluid of patients with osteoarthritis. This increase is correlated with mast cell density.²⁸

It has also been proposed that NGF may recruit more mast cells (acting as a chemoattractant). NGF may play an important role in mast cells' accumulation in non-allergic inflammatory conditions such as OA. It has been recognized for its ability to promote development and differentiation of immature mast cells.²⁴

The dysregulation of mast cells in OA has also been implicated in the structural changes of cartilage, bone, synovia, matrix, nerve endings and blood vessels.²⁸ These changes are expanded in the illustration on page 12.

The release of mast cell mediators, along with their proangiogenic and inflammatory effects, helps set the stage for joint inflammation.^{28,29}

EMERGING ROLE OF NEURONS AND NEUROGENIC INFLAMMATION

It has long been known that there is extensive crosstalk between nerves and the immune system. However, more recently this interaction is emerging as an important factor in multiple tissues effected by osteoarthritis.



The New Science of Osteoarthritis (OA) Pain and Inflammation



INFLAMMATION

Neurogenic inflammation refers to the role of sensory nerves within inflammatory disease.

NGF, interacting with its two types of receptors on sensory nerve endings, induces changes to the nerve's structure, anatomy and activity. NGF binds to the high-affinity receptor tropomyosin receptor kinase A (TrkA) (Fig. C) and the complex is internalized and moves to the cell nucleus in the dorsal root ganglion (DRG). There the complexes alter the production of different proteins (through changing transcription) including upregulating the production of neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP) (Fig. D). SP and CGRP are then released back at the peripheral nerve ending in the joint when the nerve is stimulated, increasing local inflammation (Fig. E). This NGF-mediated increase in SP and CGRP release at the periphery means that NGF-affected sensory nerves play a greater role in neurogenic inflammation than those not affected by NGF. The action of NGF is supplemented by its binding to the low-affinity neurotrophin p75 receptor (P75NTR), enabling release of these neuropeptides.^{13,28} The changes to protein production also result in an increase in neurotransmitter release at the junction between the peripheral nerve ending (first-order neuron) and the second-order neuron, facilitating transfer of the signal towards the brain.¹³

By linking all of these processes together, NGF is released from the damaged cells in the osteoarthritic joint and binds to TrkA receptors on local sensory nerves, inducing sensitization of the nociceptor. In the longer term, the retrograde migration of the NGF/TrkA complexes induces the production of pronociceptor substances that may go to both the periphery and/or the junction between the first-order neuron and second-order neuron. This one-two punch results in increased nociceptor signaling. In addition, NGF binding to TrkA receptors on immune cells results in inflammatory mediators such as histamine, PGE and NGF itself being released. This additional NGF may bind to other immune cells and/or the nociceptor, resulting in more sensitization and inflammatory mediators.³⁰

FIG. C

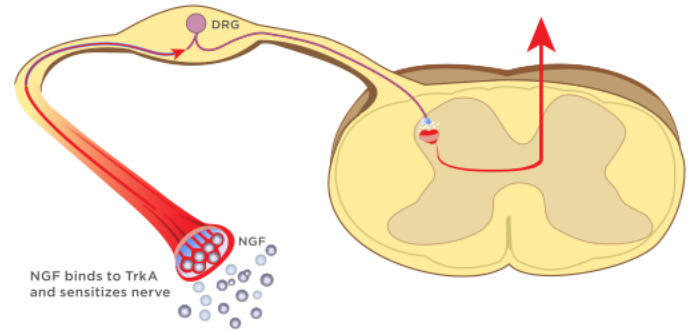


FIG. D

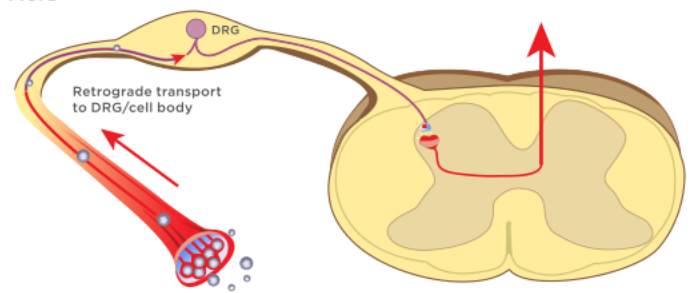
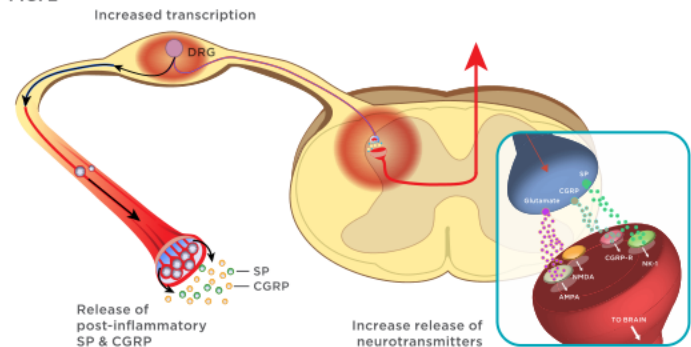


FIG. E



Images courtesy of Dr Duncan Lascelles, Translational Research in Pain (TRiP) Program, Comparative Pain Research and Education Center, North Carolina State University.





INFLAMMATION

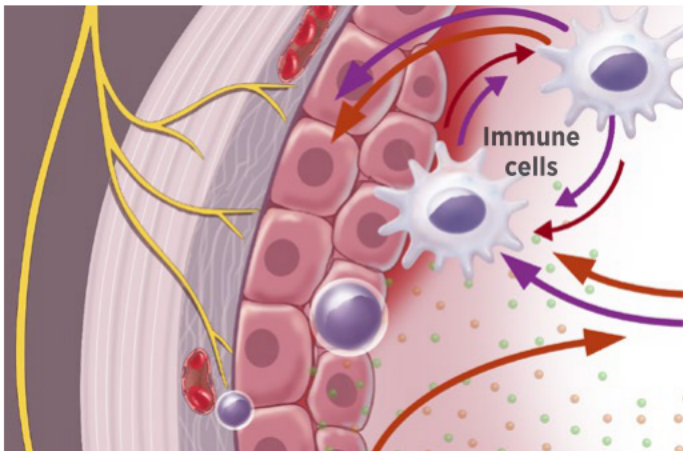
Expanded understanding of the role of joint tissues:

SYNOVIUM (SYNOVIOCYTES)

Synoviocytes exist as a 2-3 cell deep lining of the interior of the capsule that normally provides continual support through the production of synovial fluid and other factors sustaining a healthy joint.

Synovitis involves the infiltration of mononuclear cells into the synovial membrane and production of pro-inflammatory mediators, including interleukin 1β (IL- 1β), tumor necrosis factor- α (TNF- α), chemokines and NGF. Matrix metalloproteinase (MMP) -1, MMP-3 and MMP-13 as well as IL-6, can be detected in osteoarthritis synovial fluid samples (Fig. F).³¹

FIG. F



CARTILAGE (CHONDROCYTES)

Chondrocytes are the only cells found in healthy cartilage and produce and maintain the cartilaginous matrix, consisting mainly of collagens and proteoglycans. Normally, NGF is expressed at low levels by articular cartilage, but previous studies have shown that both NGF and its receptors (TrkA and P75NTR) are increased in OA articular cartilage.³²

Increased expression and secretion of NGF by synovial chondrocytes can be regulated by several factors in the OA environment, including biomechanical stress and the upregulation of pro-inflammatory mediators such as TNF- α and IL- 1β .³³ Recent studies indicate that these changes can cause the normally quiescent articular chondrocytes to undergo a phenotypic shift, leading to the disruption of homeostasis and ultimately to the aberrant expression of further pro-inflammatory and catabolic genes including aggrecanases and collagenases, especially MMP-13.

A plethora of *in vitro* models have been used by researchers but with no consensus on the most appropriate model. Models attempt to mimic factors and conditions which initiate OA, or dissect the pathways active in the disease. Underlying uncertainty as to the cause of OA and the different attributes of isolated cells and tissues used mean that similar models may produce differing results and can differ from the naturally occurring disease. The development of combinatorial models encompassing different physiological and molecular aspects of the disease should more accurately reflect the pathogenesis of the naturally occurring disease.

(Johnson CI et al)³⁴

As new therapies are developed that target the low-grade, chronic inflammation seen in OA, a critical review of the models or techniques being used to measure low-grade, chronic inflammation may be needed as opposed to the current, which are mostly high-grade acute models.





INFLAMMATION

SUBCHONDRAL BONE

Changes in the subchondral bone are extensive in OA, and a meta-analysis conducted by Barr et al, points to the existence of a robust crosstalk between subchondral bone and articular cartilage in the pathophysiology of joint diseases.^{35,36}

Thickening of the subchondral bone and osteophyte formation in OA is familiar to clinicians. Changes in the mechanical properties of the subchondral bone, and the production of inflammatory mediators by subchondral bone, can both contribute to degradation of articular cartilage.²³ Largely because of NGF,^{37,42} nerves in the subchondral bone exhibit neurite sprouting and NGF, itself and via neurogenic inflammation (and release of CGRP), induces angiogenesis. Both neurite sprouting and angiogenesis contribute to the pain and inflammation associated with the disease (Fig. G).

FIG. G



Angiogenesis

Both neurogenic inflammation and NGF itself contribute to new blood vessel development in osteoarthritis. Fusco et al wrote that experimental models “show increased vessel density in calcified cartilage, which is especially pronounced in older animals (+100%) compared to young adults [animals] (+50%).” Angiogenesis occurs in parallel with thickening of subchondral bone.²⁸

In OA, blood vessel growth has also been shown to be increased in articular cartilage, synovium and at the osteochondral junction, and angiogenesis contributes to structural progression, tissue differentiation and pain associated with disease.³⁷ The increased angiogenesis

found in the stifle joint is associated with chronic inflammation that is characterized by the release of proangiogenic factors such as VEGF, angiogenic neuropeptides and NGF.³⁷⁻³⁹

As angiogenesis and sensory nerve growth are closely linked processes that contribute to pain, the increased neovascularization likely accompanies sensory innervation into structures that are not normally innervated. Furthermore, increased binding of NGF to TrkA receptors on sensory nerve terminals may further stimulate angiogenesis, which has been demonstrated in a variety of animal models.^{40,41}

Neuron Sprouting

NGF promotes neuronal sprouting, which may increase overall sensitivity of the joint.

NGF can initiate inappropriate nerve sprouting in sensory and sympathetic nerve fibers that innervate the knee joint, contributing to increased sensitivity of individual nerves, and overall sensitivity of the joint.⁴² Several animal model studies have demonstrated that administration of NGF stimulates axonal sprouting leading to painful neuronal-like structures within the DRG and dorsal horn, suggesting that NGF-mediated nerve remodeling may contribute to chronic pain sensitivity in OA.³⁰

Angiogenesis and sensory nerve growth are closely linked processes, both occurring in the tissues of OA, and both contributing to pain and inflammation. There is strong crosstalk between nerves and blood vessels, and increased binding of NGF to TrkA receptors on sensory nerve terminals may further stimulate angiogenesis (Fig. H).³⁰

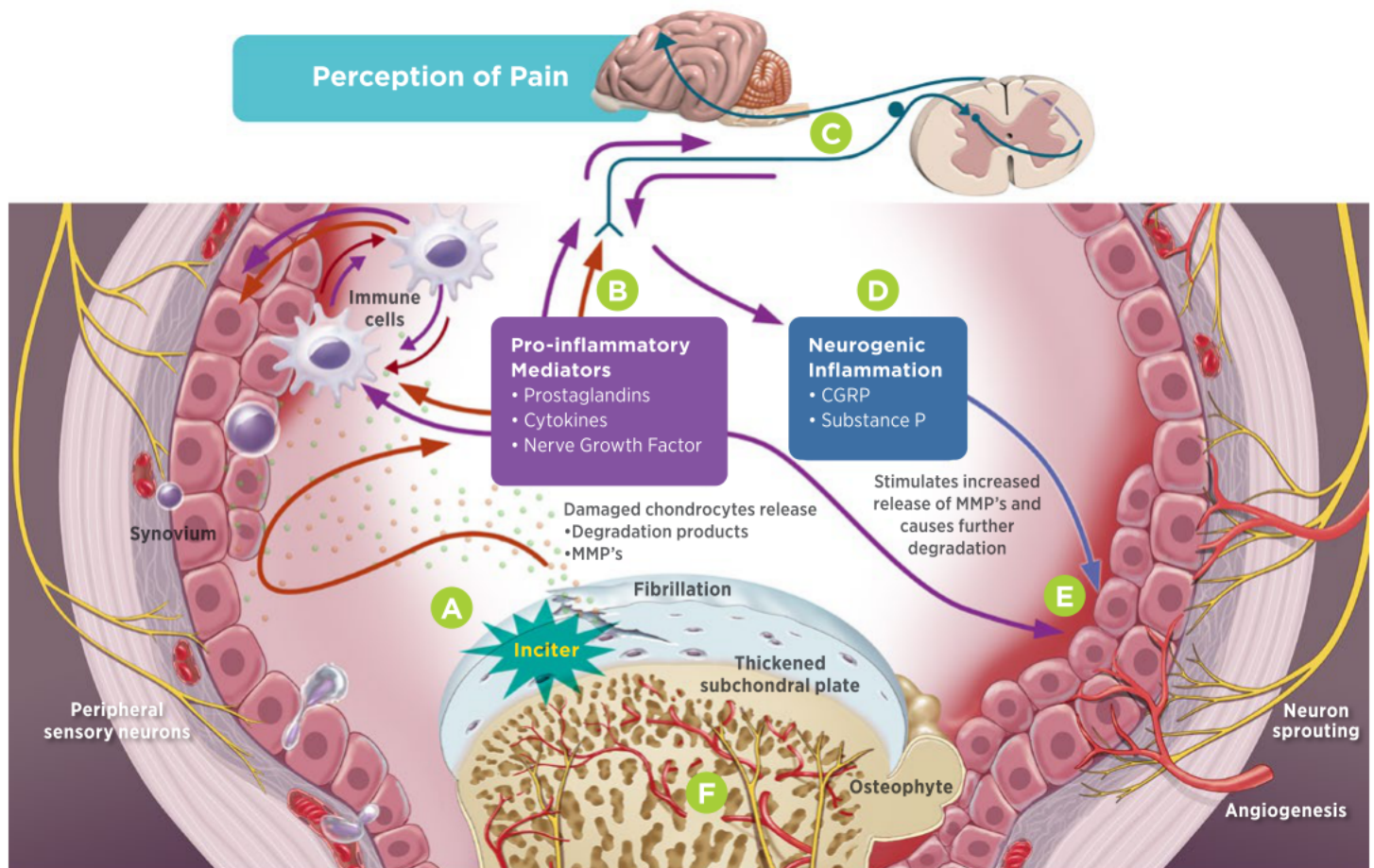
FIG. H





INFLAMMATION

CYCLE OF OSTEOARTHRITIS: PAIN AND INFLAMMATION



The New Science of Osteoarthritis (OA) Pain and Inflammation



INFLAMMATION

A. Inciter/s – Factors such as conformational abnormalities, trauma or metabolic changes initiate damage to cartilage. This damage results in the release of inflammatory mediators from chondrocytes, degradation products and matrix metalloproteinases.

B. Pro-inflammatory Mediators – The products released from damaged cartilage in turn induce synovitis that results in the release of pro-inflammatory mediators including cytokines, chemokines, PGE2 and NGF. NGF causes further inflammation of the synovium and activation of inflammatory cells. It also sensitizes nerve endings.

C. Upregulation of the Sensory Nerve – Transport of the NGF/TrkA receptor complex to the cell nucleus causes changes in transcription within the sensory nerve that results in enhanced pain signaling at both ends (peripheral and central) of the sensory nerve.

D. Neurogenic Inflammation – NGF-induced changes in the function of the peripheral nerve result in the release of pro-inflammatory mediators such as CGRP and Substance P locally from the ends of the nerve when they are activated. Release of these substances occurs at the ends of the nerve in the joint, and these substances cause inflammation—this process is called neurogenic inflammation.

E. Angiogenesis and Neuronal Sprouting – Both neurogenic inflammation and NGF itself contribute to new blood vessel development. NGF promotes neuronal sprouting, which may increase overall sensitivity of the joint. Together, these processes promote deleterious remodeling of the joint and increased joint sensitivity.

F. Cycle of Degradation – These ongoing processes lead to gradual deterioration in all components of the joint, including cartilage degradation, subchondral bone deterioration and osteophytosis.

NEW SCIENCE OF OA DISEASE SUMMARY

- ✓ OA is a highly prevalent disease in dogs and the chronic pain associated with OA negatively impacts many areas of a dog's health. Early detection and management are key.
- ✓ Chronic OA pain has a negative impact on mobility, cognitive function, affect and relationships—both human and animal.
- ✓ Inflammation in OA is low-grade and chronic, perpetuated by the loss of homeostasis leading to progressive joint destruction
- ✓ Initially considered cartilage driven, OA is now known to be a much more complex disease, with inflammatory mediators released by cartilage, bone, neurons and synovium.
- ✓ Significant crosstalk occurs among all these component tissues of the joint.
- ✓ NGF is elevated in osteoarthritic joints, and its receptors are found on immune cells. NGF is involved in neurogenic inflammation.
- ✓ Although much knowledge about inflammatory mediators in osteoarthritis has been gained in the last decade, further studies are needed to better define the mechanisms by which these factors upset the normal homeostatic processes in the joint and result in processes favoring joint degradation.





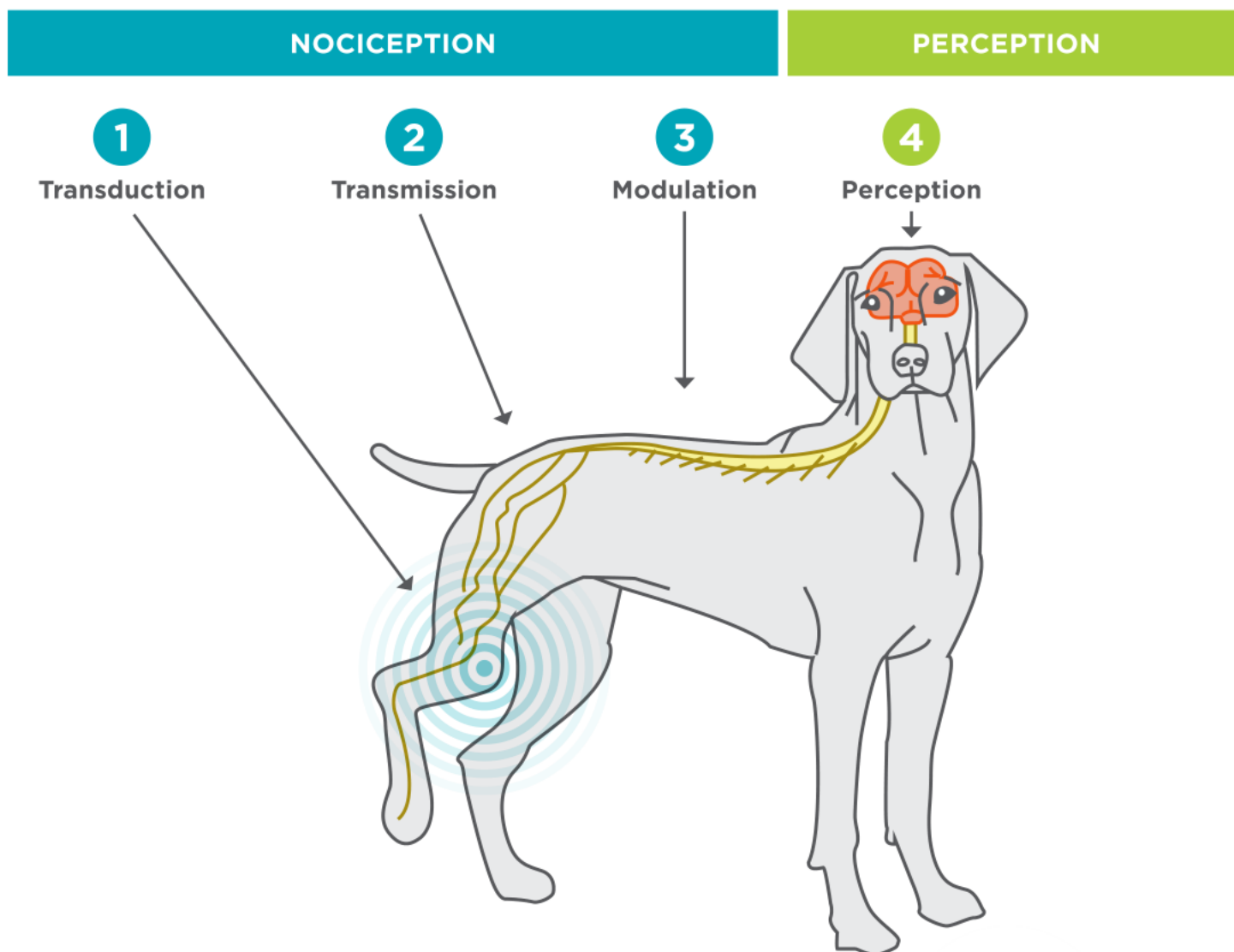
PAIN

NEW SCIENCE OF OA PAIN

As we look clinically at OA, pain remains the underlying factor that pet owners are looking to manage to improve their dog's quality of life. Nociception is part of an early learning mechanism for the protection of the animal, particularly in the acute scenario.

Nociceptors for mechanical, thermal and chemical stimuli in the periphery transduce these stimuli, initiating transmission of the signals to the brain, and resulting in a withdrawal reflex from the noxious stimuli (Fig. 1). However, in the context of chronic diseases such as OA, pain does not serve a protective function, and indeed, the changes induced in the pain transmission system are considered maladaptive and non-useful.

FIG. 1





PAIN

In addition, immune cells play a key role in pain signaling (Fig. J) in chronic OA. The balance of activity of the different signaling pathways and immune cell dysregulation results in the individual experience of pain. With so many signaling pathways and cells involved in OA pain, pain alleviation is only effective if the target is a key player amongst the multitude of processes.

NGF has been found to be a key player in pain associated with OA and is a target for both human and veterinary medicine

FIG. J: PERIPHERAL PAIN RECEPTOR SIGNALING

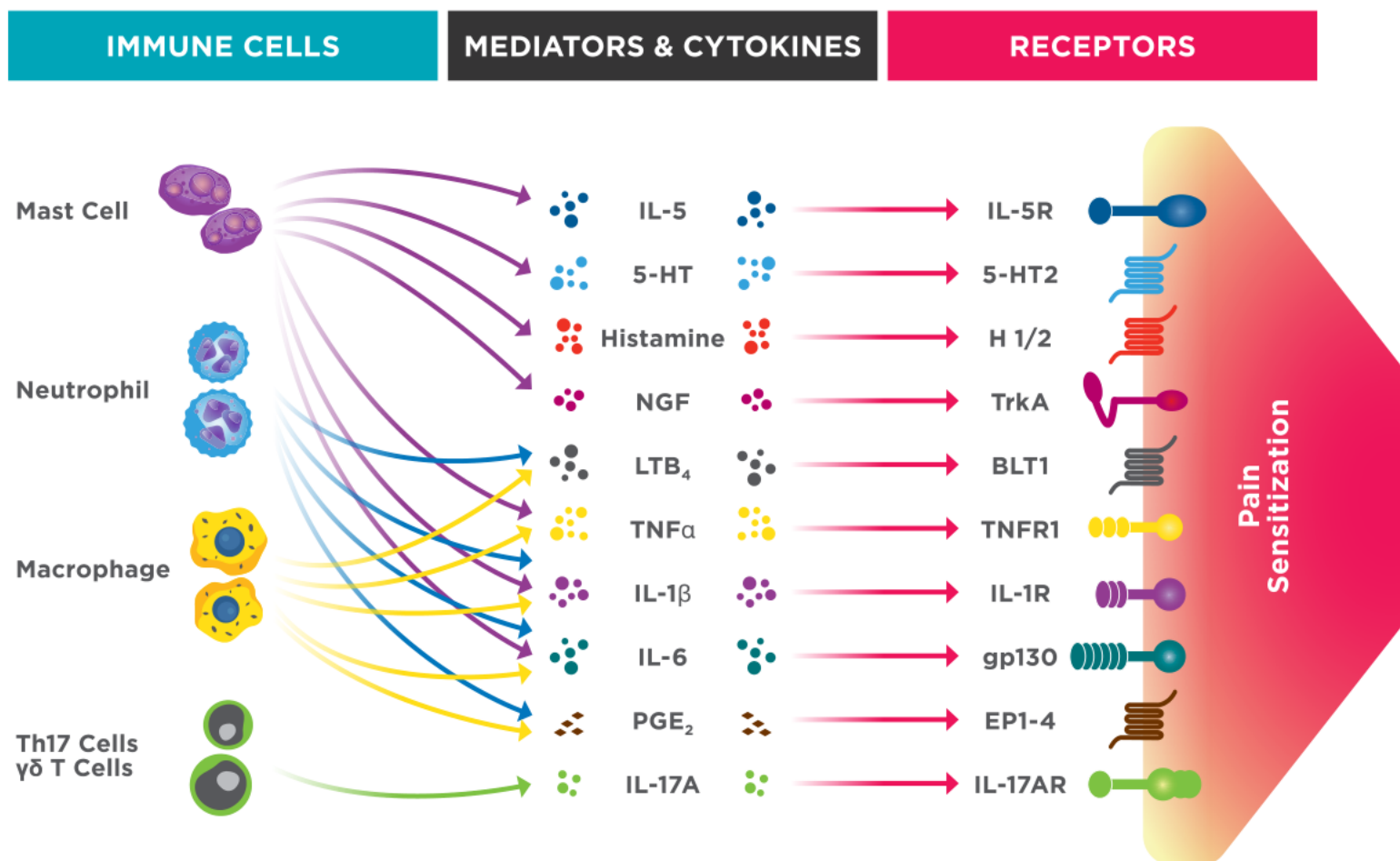


Image adapted from *Trends in Immunology*. 2017;38(1). <http://dx.doi.org/10.1016/j.it.2016.10.001>.





PAIN

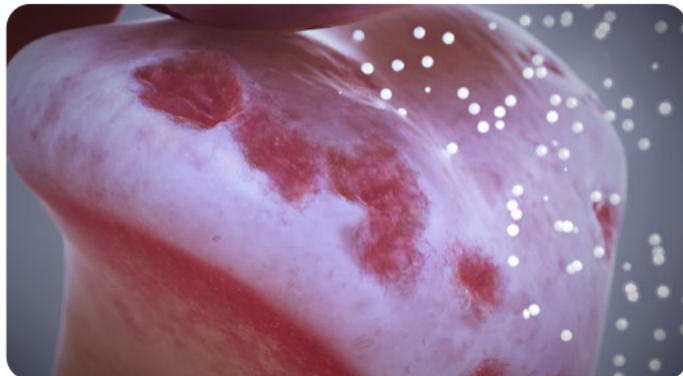
NERVE GROWTH FACTOR PLAYS A PIVOTAL ROLE IN THE PRODUCTION OF PAIN

OA pain is a complex process, mediated by many factors, including prostaglandins as well as nerve growth factor (NGF), a signaling protein that is produced by injured tissues.

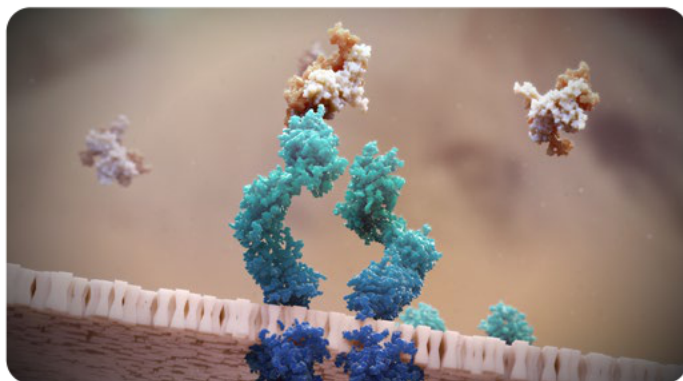
During development, nerve growth factor aids in the development of the sensory and sympathetic nervous system and plays an important role in ensuring that the nervous system develops normally. But in the adult, the primary role of NGF is pro-nociceptive that is, the production of signals, which will be interpreted as painful.

How does NGF work compared to other factors, such as prostaglandin E2 (PGE2)? PGE2 doesn't generate action potentials (nociceptive signals), but it sensitizes nerves to other molecules and that's one of the reasons inhibiting prostaglandin E2 results in effective pain relief. If you dampen down the sensitization of nerves, you're going to dampen down the ability of these other molecules to activate those nerves.

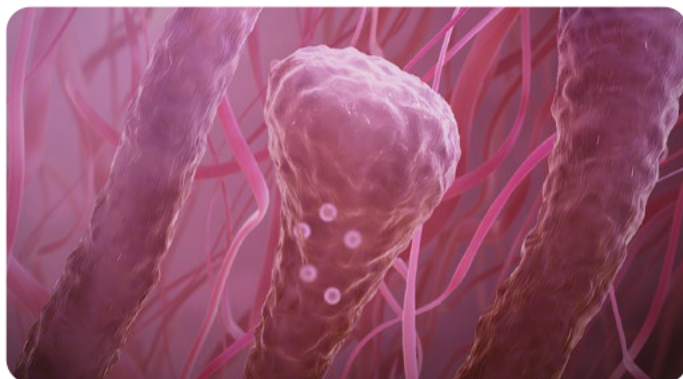
NGF does a very similar thing. It sensitizes nerves, but in addition, nerve growth factor also alters the phenotype of nerves. It alters the expression of pain receptors and the amount of neurotransmitters these nerves are producing. **So, you can think of NGF as very similar in its actions to prostaglandin E2 with the addition that it also changes the nerves in a way that makes them more responsive and that makes them respond more strongly to pain signals.**



NGF is elevated in synovial fluid in joints with osteoarthritis (but not in healthy joints).



The binding of NGF to TrkA pain receptors increases overall sensitization to local painful stimuli.



After binding, NGF-TrkA complexes are internalized and migrate to the nerve cell body. There, the complexes direct activities that alter the function of the nerve and sensitize it to pain stimuli, making it a good target for intervention.



The New Science of Osteoarthritis (OA) Pain and Inflammation



PAIN

NEW SCIENCE OF OA PAIN

New scientific innovations allow for the creation of monoclonal antibody therapy (mAbs) designed specifically for feline and canine use.

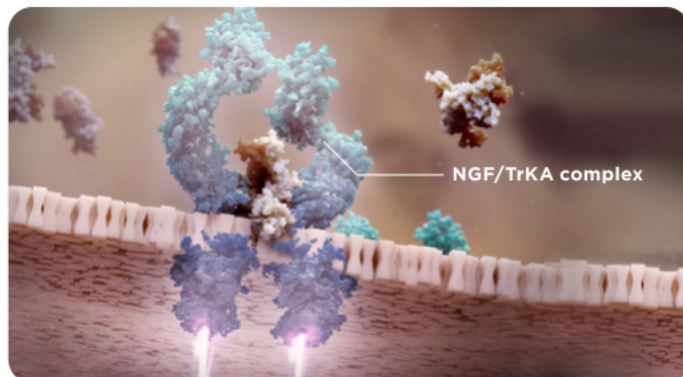
Clinical researchers have found that it is now possible to lower NGF's negative influence on pain with anti-NGF antibody therapies.^{43,44} These species-specific therapies are designed to be long-acting (about a month) and are delivered via subcutaneous injection.

Antibodies are metabolized differently than small molecules—they are metabolized to peptides and amino acids within cells. As such, they are expected to have a different safety profile than traditional drug therapies.⁴⁵

ANTI-NGF ANTIBODY THERAPY MAY PROVIDE VETERINARIANS A POWERFUL NEW ALTERNATIVE FOR THE TREATMENT OF OA PAIN

Anti-NGF mAbs are designed to effectively:

- Reduce pain signals by preventing NGF from binding to, and activating, TrkA receptors
- Lower the amount of NGF within the joint available to bind to immune cells
- Be non-narcotic, non-sedating
- Sustain pain reduction delivered for about a month in both canine and feline proof of concept studies^{43,44}



Watch the NGF video at TheNewScienceofOAPain.com

WATCH NGF MOA VIDEO

PAVING THE WAY FOR A NEW CLASS OF PAIN THERAPIES

The potential for anti-NGF antibody therapy to control OA pain is an exciting new development and represents the first new medication class innovation identified to block pain outside the prostaglandin pain pathway in over 20 years.

Anti-NGF antibody therapy may come to represent a new class of veterinary medications and may be an effective new way for veterinarians to provide safe, long-lasting control of chronic pain to both cats and dogs.





1. <https://www.oarsi.org/research/standardization-osteoarthritis-definitions> (accessed February 24, 2020).
2. Johnston S. *Vet Clinics of NA*. 1997;27(4).
3. Wright A, Amodie DM, Cernicchiaro N, Lascelles BDX, Pavlock AM. Diagnosis and treatment rates of osteoarthritis in dogs using a Health Risk Assessment (HRA) or Health Questionnaire for Osteoarthritis in general veterinary practice. *ISPOR*. 2019.
4. Foster Rosenblatt. Global Veterinarian Market Research. 2020.
5. Lascelles BDX, Brown DC, Conzemius MG, Gill M, Oshinsky ML, Sharkey M. Measurement of chronic pain in companion animals: discussions from the Pain in Animals Workshop (PAW) 2017. *The Veterinary Journal*. 2019;50:71-78.
6. Sanderson RO, Beata C, Flipo RM, Genevois JP, Macias C, Tacke S, Vezzoni A, Innes JF. Systematic review of the management of canine osteoarthritis. *Veterinary Record*. 2009;164(14):418-424.
7. Lascelles BDX, Gaynor JS, Smith ES, Roe SC, Marcellin-Little DJ, Davidson G, Boland E, Carr J. Amantadine in a multimodal analgesic regimen for alleviation of refractory osteoarthritis pain in dogs. *Journal of Veterinary Internal Medicine*. 2008;22(1):53-59.
8. Lascelles BDX, Court MH, Hardie EM, Robertson SA. Nonsteroidal anti-inflammatory drugs in cats: a review. *Veterinary Anaesthesia and Analgesia*. 2007;34(4):228-250.
9. Rychel JK. Diagnosis and treatment of osteoarthritis. *Topics in Companion Animal Medicine*. 2010;25(1):20-25.
10. Marino CL, Lascelles BDX, Vaden SL, Gruen ME, Marks SL. Prevalence and classification of chronic kidney disease in cats randomly selected from four age groups and in cats recruited for degenerative joint disease studies. *Journal of Feline Medicine and Surgery*. 2014;16(6):465-472.
11. Belshaw Z, Asher L, Dean RS. The attitudes of owners and veterinary professionals in the United Kingdom to the risk of adverse events associated with using non-steroidal anti-inflammatory drugs (NSAIDs) to treat dogs with osteoarthritis. *Preventive Veterinary Medicine*. 2016;131:121-126.
12. American Animal Hospital Association (ed). *Compliance: Taking Quality Care to the Next Level; A Report of the 2009 AAHA Compliance Follow-Up Study*. American Animal Hospital Association. 2009.
13. Enomoto M, Mantyh PW, Murrell J, Innes JF, Lascelles BDX. Anti-nerve growth factor monoclonal antibodies for the control of pain in dogs and cats. *The Veterinary Record*. 2019;184(1):23.
14. KG MARKETSENSE. Global Pet Owner Market Research. 2018.
15. KuKanich B. Outpatient oral analgesics in dogs and cats beyond nonsteroidal antiinflammatory drugs: an evidence-based approach. *Veterinary Clinics: Small Animal Practice*. 2013;43(5):1109-1125.
16. Budsberg SC, Torres BT, Kleins SA, Sandberg GS, Berjeski AK. Lack of effectiveness of tramadol hydrochloride for the treatment of pain and joint dysfunction in dogs with chronic osteoarthritis. *Journal of the American Veterinary Medical Association*. 2018;252(4):427-432.
17. Moore GE, Burkman KD, Carter MN, Peterson MR. Causes of death or reasons for euthanasia in military working dogs: 927 cases (1993-1996). *Journal of the American Veterinary Medical Association*. 2001;219(2):209-214.
18. Lawler DF, Evans RH, Larson BT, Spitznagel EL, Ellersieck MR, Kealy RD. Influence of lifetime food restriction on causes, time, and predictors of death in dogs. *Journal of the American Veterinary Medical Association*. 2005;226(2):225-231.
19. Innes JF. Arthritis (chap 68). In: *Veterinary Surgery: Small Animal Expert Consult - E-BOOK*. 2017.
20. Nettelbladt EG, Sundblad LK. Protein patterns in synovial fluid and serum in rheumatoid arthritis and osteoarthritis. *Arthritis & Rheumatology*. 1959;2(2):144-151.
21. Sokolove J, Lepus CM. Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. *Therapeutic Advances in Musculoskeletal Disease*. 2013;5(2):77-94.
22. Isol M, Ferrari V, Miolo A, Stabile F, Bernardini D, Carnier P, Busetto, R. Nerve growth factor concentrations in the synovial fluid from healthy dogs and dogs with secondary osteoarthritis. *Veterinary and Comparative Orthopaedics and Traumatology*. 2011;24(4):279-284.
23. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). *Osteoarthritis and Cartilage*. 2013;21(1):16-21.
24. Gigante A, Farinelli L, Manzotti S, Aquili A, Papalia G. *Synovial Mast Cells in Osteoarthritis*. 2018.
25. Haseeb A, Haqqi TM. Immunopathogenesis of osteoarthritis. *Clinical Immunology*. 2013;146(3):185-196.
26. Robinson WH, Lepus CM, Wang Q, Raghu H, Mao R, Lindstrom TM, Sokolove J. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. *Nature Reviews Rheumatology*. 2016;12(10):580-592.
27. De Lange-Brokaar BJ, Ioan-Facsinay A, Van Osch GJ, Zuurmond AM, Schoones J, Toes RE, Huizinga TW, Kloppenburg M. Synovial inflammation, immune cells and their cytokines in osteoarthritis: a review. *Osteoarthritis and Cartilage*. 2012;20(12):1484-1499.
28. Fusco M, Skaper SD, Coaccioli S, Varrassi G, Paladini A. Degenerative joint diseases and neuroinflammation. *Pain Practice*. 2017;17(4):522-532.
29. Wang Q, Lepus CM, Raghu H, Reber LL, Tsai MM, Wong HH, von Kaeppler E, Lingampalli N, Bloom MS, Hu N, Elliott, EE. IgE-mediated mast cell activation promotes inflammation and cartilage destruction in osteoarthritis. *Elife*. 2019;8:e39905.
30. Schmelz M, Mantyh P, Malfait AM, Farrar J, Yaksh T, Tive L, Viktrup L. Nerve growth factor antibody for the treatment of osteoarthritis pain and chronic low-back pain: mechanism of action in the context of efficacy and safety. *Pain*. 2019;160(10):2210.
31. Goldring MB, Otero M. Inflammation in osteoarthritis. *Current Opinion in Rheumatology*. 2011;23(5):471.
32. Iannone F, De Bari C, Dell'Accio F, Covelli M, Patella V, Lo Bianco G, Lapadula G. Increased expression of nerve growth factor (NGF) and high affinity NGF receptor (p140 TrkA) in human osteoarthritic chondrocytes. *Rheumatology*. 2002;41(12):1413-1418.
33. Pecchi E, Priam S, Gosset M, Pigenet A, Sudre L, Laiguillon MC, Berenbaum F, Houard X. Induction of nerve growth factor expression and release by mechanical and inflammatory stimuli in chondrocytes: possible involvement in osteoarthritis pain. *Arthritis Research & Therapy*. 2014;16(1):1-11.
34. Johnson CI, Argyle DJ, Clements DN. In vitro models for the study of osteoarthritis. *The Veterinary Journal*. 2016;209:40-49.
35. Barr AJ, Campbell TM, Hopkinson D, Kingsbury SR, Bowes MA, Conaghan PG. A systematic review of the relationship between subchondral bone features, pain and structural pathology in peripheral joint osteoarthritis. *Arthritis Research & Therapy*. 2015;17(1):228.
36. Pan B, Wang B, Li W, Zhou X, Scherr T, Yang Y, Price C, Wang L. Elevated cross-talk between subchondral bone and cartilage in osteoarthritic joints. *Bone*. 2012;51(2):212-217.
37. Mapp PI, Walsh DA. Mechanisms and targets of angiogenesis and nerve growth in osteoarthritis. *Nature Reviews Rheumatology*. 2012;8(7):390.
38. Seegers HC, Hood VC, Kidd BL, Cruwys SC, Walsh DA. Enhancement of angiogenesis by endogenous substance P release and neurokinin-1 receptors during neurogenic inflammation. *Journal of Pharmacology and Experimental Therapeutics*. 2003;306(1):8-12.
39. Walsh DA, McWilliams DF, Turley MJ, Dixon MR, Fransès RE, Mapp PI, Wilson D. Angiogenesis and nerve growth factor at the osteochondral junction in rheumatoid arthritis and osteoarthritis. *Rheumatology*. 2010;49(10):1852-1861.
40. Cantarella G, Lempereur L, Presta M, Ribatt, D, Lombardo G, Lazarovici P, Zappala G, Pafumi C, Bernardini R. Nerve growth factor-endothelial cell interaction leads to angiogenesis in vitro and in vivo. *The FASEB Journal*. 2002;16(10):1307-1309.
41. Lazarovici P, Gazit A, Staniszevska I, Marcinkiewicz C, Leikes PI. Nerve growth factor (NGF) promotes angiogenesis in the quail chorioallantoic membrane. *Endothelium*. 2006;13(1):51-59.
42. Jimenez-Andrade JM, Mantyh PW. Sensory and sympathetic nerve fibers undergo sprouting and neuroma formation in the painful arthritic joint of geriatric mice. *Arthritis Research & Therapy*. 2012;14(3):R101.
43. Lascelles BDX, Knazovicky D, Cas B, Freire M, Innes JF, Drew AC, Gearin DP. A canine-specific anti-nerve growth factor antibody alleviates pain and improves mobility and function in dogs with degenerative joint disease-associated pain. *BMC Veterinary Research*. 2015;11(1):101.
44. Gruen ME, Thomson AE, Griffith EH, Paradise H, Gearing DP, Lascelles BDX. A feline-specific anti-nerve growth factor antibody improves mobility in cats with degenerative joint disease-associated pain: a pilot proof of concept study. *Journal of Veterinary Internal Medicine*. 2016;30(4):1138-1148.
45. Olivry T et al. Advances in veterinary medicine: therapeutic monoclonal antibodies for companion animals. *Clin Notes*. March 10, 2015. https://www.zoetisus.com/conditions/dogs/itchcycle/downloads/resources/publications/zoetiscn_mar_fnl.pdf. Accessed May 3, 2019.





THE NEW SCIENCE OF CANINE OA PAIN

NEW SCIENCE OF OA PAIN AND INFLAMMATION – SUMMARY

- ✓ Osteoarthritis continues to be a significant disease for humans and dogs alike.
- ✓ Chronic OA pain has a negative impact on mobility, cognitive function, affect and relationships—for both humans and animals.
- ✓ The lack of new products to help manage the pain associated with OA has been a gap for over 20 years in both human and veterinary medicine.
- ✓ OA in dogs is often under-diagnosed. Early identification and treatment of OA pain can help improve a dog's quality of life.
- ✓ Inflammation in OA is low-grade and chronic, perpetuated by the loss of homeostasis leading to progressive joint destruction.
- ✓ Initially considered cartilage driven, OA is now known to be a much more complex disease, with inflammatory mediators released by cartilage, bone, neurons and synovium.
- ✓ NGF is elevated in osteoarthritic joints, and its receptors are found on immune cells. NGF is also involved in neurogenic inflammation.
- ✓ NGF has been found to be a key player in pain associated with OA and is a potential new target for both human and veterinary medicine.
- ✓ NGF sensitizes nerves but also changes the nerves in a way that makes them more responsive and that makes them respond more strongly to pain signals.
- ✓ Anti-NGF antibody therapies are in development. They may be an effective new alternative for veterinarians to provide safe, long-lasting control of chronic pain to both dogs and cats.