

# **New Insights Into Canine and Feline OA Pain:**

Anti-NGF mAb Offers Promising  
Novel Therapy

**OA PAIN ADVISORY BOARD 2020 PROCEEDINGS**



# SUMMARY

## Anti-NGF mAb therapy shows promise for safely and effectively managing OA-associated pain in both canine and feline patients.

Osteoarthritis disease is first and foremost experienced as pain. When introduced, nonsteroidal anti-inflammatory drugs (NSAIDs) provided a breakthrough in the ability to manage osteoarthritis (OA) pain in dogs. NSAIDs are currently the cornerstone of canine OA treatment; however, gaps exist when it comes to providing consistent, profound OA pain relief. In addition, no FDA-approved therapies exist for the treatment of chronic pain in cats. This has left many practitioners with few approved options for their OA patients, many painful pets undertreated or untreated, and many pet owners frustrated.

New scientific knowledge has revealed the important role of nerve growth factor (NGF) as a powerful mediator of OA pain. The ability to target this key component of the pain pathway using monoclonal antibody (mAb) therapy will give veterinarians a novel option for providing long-lasting control of OA pain to dogs and cats.



# MEET THE EXPERTS

## 2020 OA PAIN Advisory Board Members

A panel of experts was convened to provide practitioners with an updated understanding of the mechanisms of OA pain, the value of proven effective analgesia in OA pain management, and a look ahead at a potential future treatment.



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# TABLE OF CONTENTS

## Chapter I

The New Science of OA Pain: An Updated Understanding of Pain Progression

A Closer Look at Proinflammatory Mediators	2
Nerve Growth Factor: A Novel Therapeutic Target in OA Pain Management	2
The Role of NGF in OA Pain	2
Neurogenic vs. Classic Inflammation	5

## Chapter II

The Impact of Chronic Pain on Pets

The Patient Experience of OA Pain	7
Challenges in the Current Approach to OA Pain Management	7

## Chapter III

The Next Breakthrough in OA Pain Relief: An Innovative New Treatment

Anti-NGF mAb Therapy	11
Anti-NGF mAb for Canine OA Pain Control	12
Anti-NGF mAb for Feline OA Pain Control	12
Supporting the Human-Animal Bond: A Win for the Pet, Owner, and Veterinarian	13





## CHAPTER I

# The New Science of OA Pain: An Updated Understanding of Pain Progression

## A Closer Look at Proinflammatory Mediators

Cartilage damage in the joint initiates osteoarthritis (OA) by leading to the release of proinflammatory mediators; these mediators include prostaglandins, neuropeptides, cytokines, and neurotrophins. This damage additionally sparks the release of mast cells, neutrophils, macrophages, and other immune cells, all of which also release more proinflammatory mediators, leading to an ongoing cycle of pain and inflammation.

Since the introduction of nonsteroidal anti-inflammatory drugs (NSAIDs), veterinary medicine has focused on providing OA pain relief through the reduction of prostaglandins, specifically prostaglandin E<sub>2</sub> (PGE<sub>2</sub>). However, in recent years, research has begun concentrating on the role of other mediators and their potential as effective targets of analgesic therapy, mirroring what has been studied in human medicine. As Dr. Sheilah Robertson points out, “Osteoarthritis is a terribly complex disease, so it’s just not as simple as that. Although the prostaglandins are involved in causing the pain and some of the inflammation that goes on in the joint, they’re not necessarily the key player.”

“We think of straightforward inflammation as the generator of pain for OA, but there are quite a few pain generators, including nerve growth factor (NGF),” says Dr. Tamara Grubb. “We’ve focused on just standard inflammation for such a long time because that’s all we could treat. But now we’re focusing more on some of the other opportunities for treatment [of OA pain].”

Specific proinflammatory mediators that play a role in OA-associated pain include:

- PGE<sub>2</sub>, a prostaglandin
- Calcitonin gene-related peptide (CGRP) and substance P, both neuropeptides (neurotransmitters) that are released from sensory nerves
- NGF, a neurotrophin

“Prostaglandins are potent generators of pain and important to control,” Dr. Grubb explains. “But from everything that we can see right now, NGF is actually a more potent driver of pain, including OA pain.”

## Nerve Growth Factor: A Novel Therapeutic Target in OA Pain Management

A naturally occurring protein, NGF plays an important role in the development of neurons early in life, both pre- and postnatally. In the adult, NGF is a signaling protein released in injured tissues that initiates the pain signal and then contributes to a cycle of pain and inflammation. To view a 3-minute video of NGF activity in the joint and the anti-NGF monoclonal mechanism of action, visit [ngfcatsdogs.com](http://ngfcatsdogs.com).

“When you talk about the myriad of things involved [in OA pain], they’re not all equally important,” Dr. B. Duncan X. Lascelles says. “If you inhibit NGF, you see a clinical result.”

*“As our understanding of the biochemistry [of OA] becomes more and more vivid, we’re now being able to see targets of opportunity that we can attack, and NGF is a classic example of that. It’s released from a variety of places, and it has detrimental effects, [so we looked into]: Can we either stop its release or sequester it?”*

– Dr. Budsberg

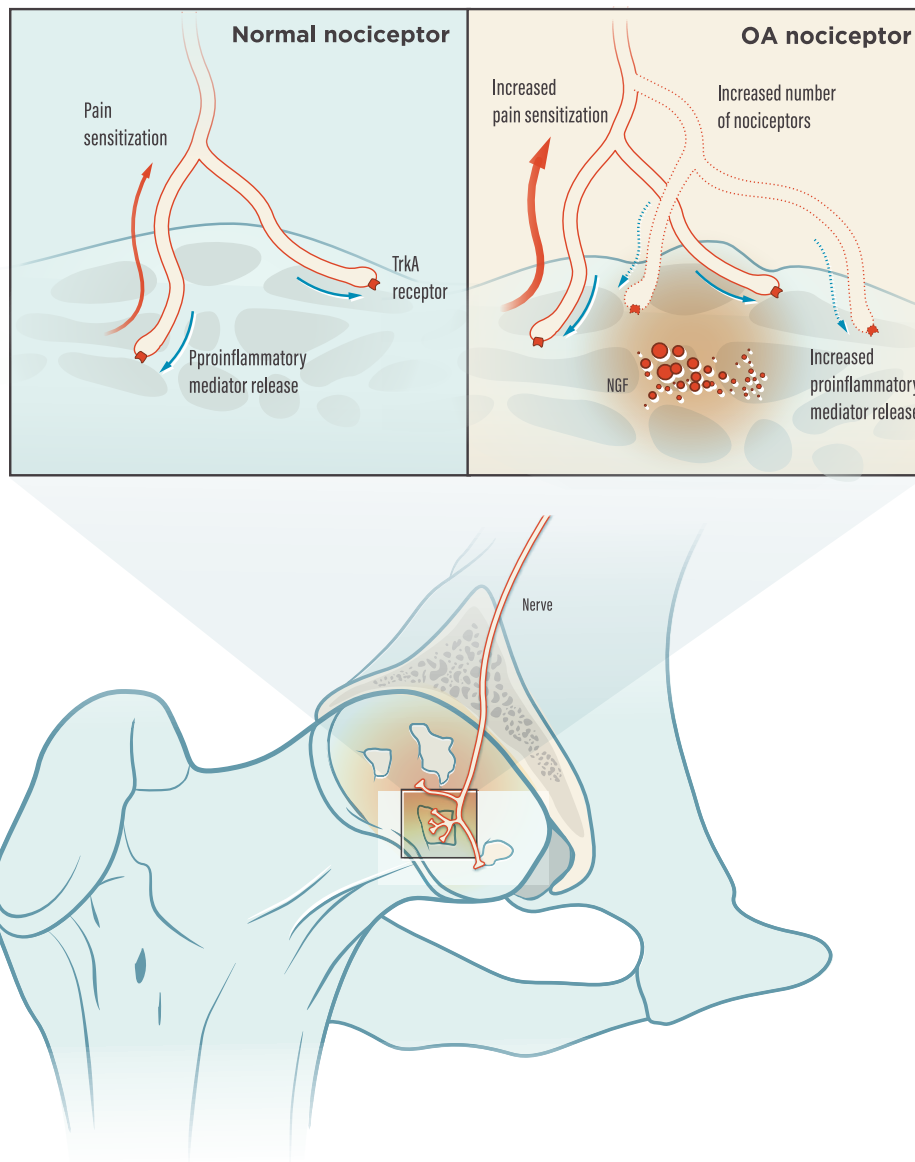
## The Role of NGF in OA Pain

Both PGE<sub>2</sub> and NGF are released from damaged tissues in the osteoarthritic joint:

- PGE<sub>2</sub> binds to prostaglandin EP<sub>1-4</sub> receptors.
- NGF binds to the NGF-specific tropomyosin receptor kinase A (TrkA).

## Figure 1. NGF phenotypically changes the nerve

When it binds to its receptor (TrkA), NGF alters the nerve's look and function (changes its phenotype). NGF, nerve growth factor; TrkA, tropomyosin receptor kinase A.



NGF and PGE<sub>2</sub> both activate the nervous system locally (causing peripheral sensitization in the nerves that innervate the joint) and centrally. But NGF does more than just cause sensitization; it also causes phenotypic (physical and biochemical) changes in the nerve (**Figure 1**).

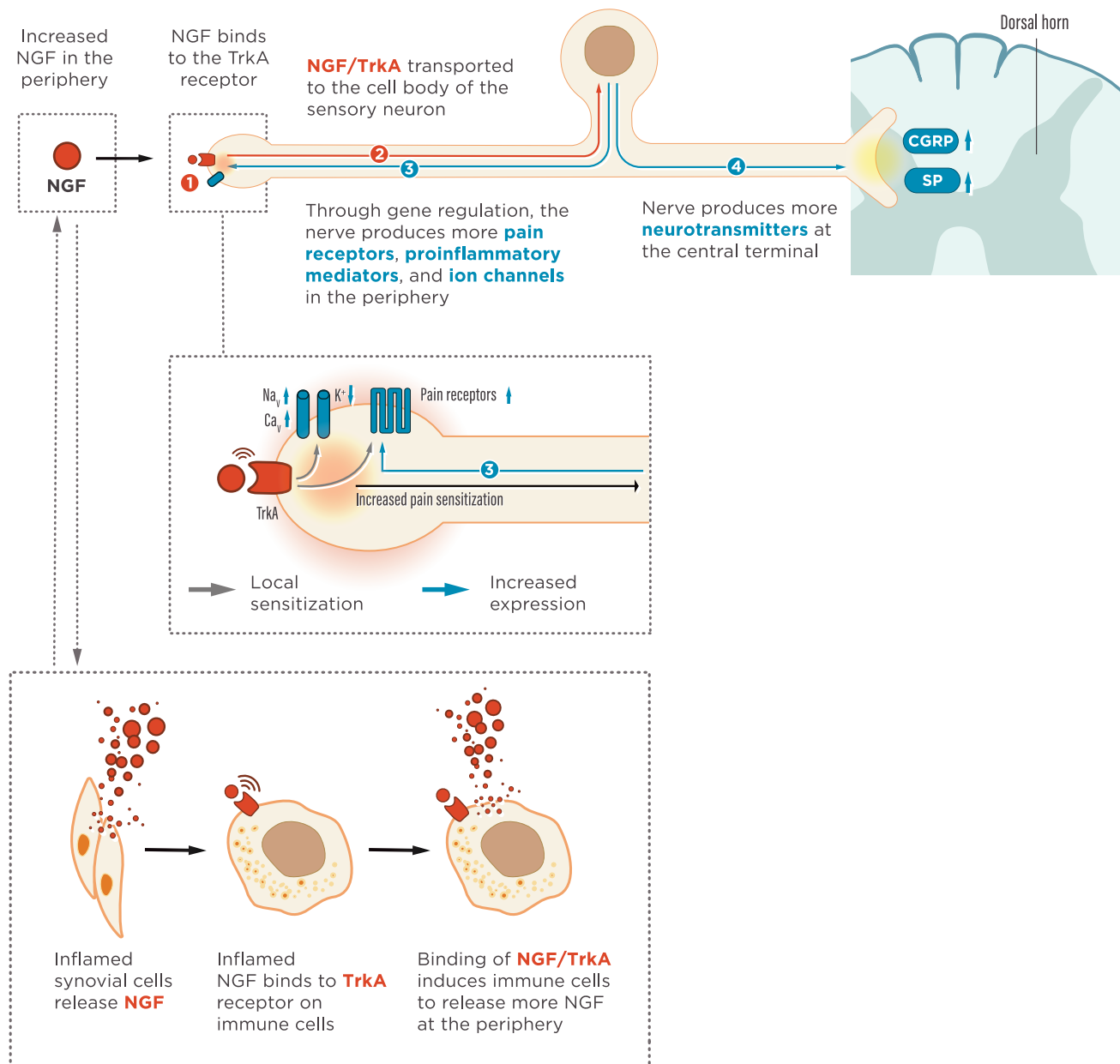
*“There’s very robust evidence to show that NGF changes the phenotype—the look and function—of the peripheral sensory nerve. And because of those phenotypic changes, that NGF-affected nerve is now participating, to a greater degree, in peripheral sensitization and central sensitization. So essentially, those changes in the periphery are driving more pain and greater sensitivity in those patients, ultimately leading to greater disability.”*

– Dr. Lascelles

## Figure 2. Overview of NGF's role in nociception

### A. Like PGE<sub>2</sub>, NGF increases a nerve's sensitivity due to sensitizing receptors at the nerve ending ①

But NGF does more: When it binds to its receptor (TrkA), the complex is then retrogradely transported to the cell body ② Here, NGF contributes to local and chronic pain signaling by altering the transcription of receptors and neurotransmitters. Increased pain receptors, proinflammatory mediators and ion channels are produced and sent to the periphery of the nerve ③ Additionally, more neurotransmitters are produced and sent to the central terminal of the nerve ④ Together, all these changes increase the contribution of the sensory nerve to local sensitization and inflammation, central sensitization, and a heightened sensation of pain. CA<sub>v</sub>, voltage-gated calcium channel; CGRP, calcitonin gene-related peptide; K<sup>+</sup>, potassium channel; NA<sub>v</sub>, voltage-gated sodium channel; NGF, nerve growth factor; SP, substance P; TrkA, tropomyosin receptor kinase A.



### B. Tissue damage increases amount of NGF in the periphery

NGF is released by damaged tissues and immune cells through a self-perpetuating cycle.



Both  $\text{PGE}_2$  and NGF play similar roles in the pain of OA, but NGF “takes the effects of  $\text{PGE}_2$  to another level,” says Dr. Lascelles (**Figure 2A**).

NGF also binds to TrkA receptors on mast cells and other immune/inflammatory cells, leading to the release of more NGF. In other words, the presence of NGF in OA patients creates a feedback loop that increases and perpetuates pain (**Figure 2B**).

### Neurogenic vs. Classic Inflammation

*“OA is not just a problem in the joint. What we’re now learning so much more about is that something that we call ‘neurogenic inflammation’ is a key component to this whole picture.”*

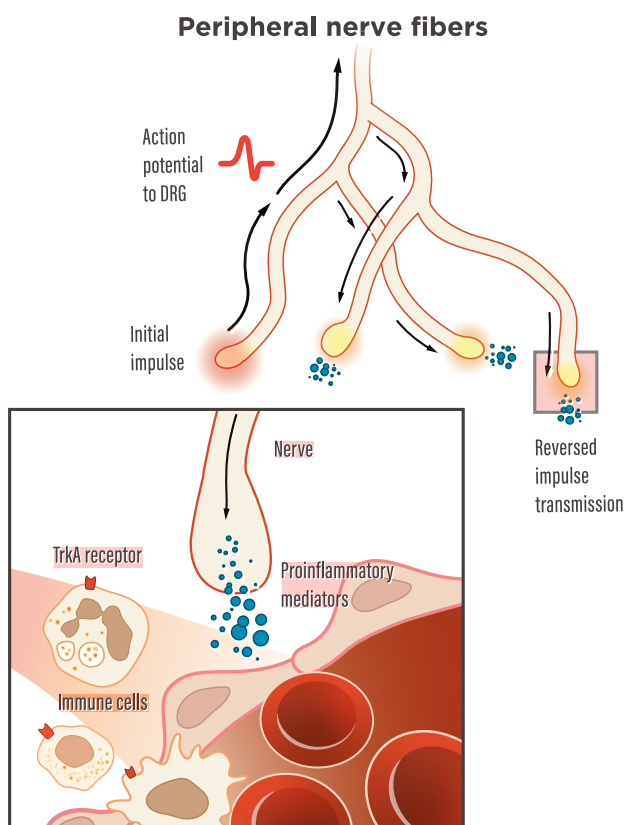
– Dr. Robertson

Neurogenic inflammation (**Figure 3**) is initiated by activation of the peripheral nervous system rather than by immunologic events. When NGF is released in OA, it stimulates neurogenic inflammation. The resulting phenotypic change to the nerve drives much of the pain of OA.

“We’re actually trying to calm down the nervous system, not the traditional view that we’ve all had of inflammation. It’s a very different way of looking at this disease,” Dr. Robertson says. “The data would support that we’ve been missing a big target for a long time.”

### Figure 3. Neurogenic inflammation

Activation of nociceptors results not only in impulse transmission towards the spinal cord, but as impulses reach nerve branches, they can also propagate back toward the periphery (antidromic direction). When these antidromic impulses reach the periphery, they result in the release of proinflammatory transmitters from the ends of the nerves. These proinflammatory neurotransmitters can also recruit and activate immune cells in the vicinity. DRG, dorsal root ganglion; TrkA, tropomyosin receptor kinase A.



Watch Dr. Lascelles explaining the effects of NGF here:

[www.thenewscienceofpain.com](http://www.thenewscienceofpain.com)

from the experts



## CHAPTER II

# The Impact of **Chronic Pain** on Pets





Watch Dr. Grubb and Dr. Robertson explaining pain from a pet's perspective:

[www.thenewscienceofopain.com](http://www.thenewscienceofopain.com)

## from the experts

### The Patient Experience of OA Pain

#### The Wide-Reaching Effects of Pain

*“Pain has a body-wide impact. It doesn’t exist in a vacuum. It’s not just ‘ouch.’ There are numerous negative consequences of pain.”*

– Dr. Grubb

Dogs and cats experience the disease of OA through pain. In OA, there are components of adaptive and maladaptive pain. “The adaptive pain signal in the joint remains there to tell the [pet] that the area is painful,” Dr. Margaret E. Gruen explains. “But the maladaptive components—the generalized sensitization, the changes in affect and mood and social interaction—can start very quickly.”

#### Effects of Pain on the Human-Animal Bond

*“A cat or a dog lives [in the] here and now, so every day has to be good.”*

– Dr. Robertson

Pain has profound effects on the body. It’s more than just sensory. Pain involves an emotional component as well, potentially leading to fear, anxiety, and stress (FAS), which can negatively affect a dog or cat’s relationship with the owner. FAS also heightens the sensation of pain.

Paradoxically, current treatments for OA pain in the dog and cat require daily oral dosing,

which can lead to owner aversion and damage the human-animal bond.

“If you’re in a state of anxiety and stress, then pain is worse,” says Dr. Robertson. “Owner aversion is something that cats develop. If you come up with this great plan, and it’s 6 drugs 3 times a day, and the cat hates its life and hates you and runs and hides, now you not only can’t get the drugs in, but you break the human-animal bond at that point.”

### Challenges in the Current Approach to OA Pain Management

#### Use of NSAIDs in OA Pain

*“We know NSAIDs don’t completely control pain of osteoarthritis.”*

– Dr. Grubb

Traditional NSAIDs work by inhibiting the activity of cyclooxygenase enzymes (COX-1 and/or COX-2), which are responsible for producing PGE<sub>2</sub> and other prostaglandins. The newer piperant class of NSAIDs is non-COX-inhibiting and instead selectively blocks prostaglandins from binding to the EP<sub>4</sub> receptor. The clinical impact of either mechanism of action is to effectively decrease pain by diminishing peripheral sensitization, and is foundational to the multimodal protocol.

The challenge with long-term NSAID use can be the development of breakthrough pain. That is the gap in OA pain management.

In addition, for cats, there is no FDA-approved NSAID option for chronic pain in the United States.

To help dog and cat owners identify their pets' activities and behaviors that might be a sign of OA, refer them to one of these checklists:

Cat owners:  
[catoacheklist.com](http://catoacheklist.com)

Dog owners:  
[dogoacheklist.com](http://dogoacheklist.com)

## the new science of OA



### Lack of Pain Recognition by Pet Owners

*"When we only treat pain intermittently, often the reason that it's done is because the owner is looking at the pet, saying, 'It's not such a bad day. We don't have to worry about it.'"*

– Dr. Petty

Many owners fail to recognize the problem, even when their pets have reduced mobility, often chalking it up to the pet "slowing down with age." However, there are consequences to delayed OA pain management.

"If we delay the treatment of OA, the animal loses muscle mass. Muscle is important for joint support and for exercise," Dr. Michael Petty says. "If they can't exercise, then they gain weight, and the weight causes an increase in the pressure on the joints. This makes the animal much more painful and much harder to treat."

"We all know the sooner we catch this disease by early screening, the better a job we can do at protecting the nervous system, protecting the joint, and preventing all that damage," says Dr. Robertson.

"My worry is that people don't recognize that their cats are uncomfortable right now," Dr. Gruen says. "[If cat owners understand that their cats can get help with OA pain], they'll be excited that their cats can do those things again and will really want to keep them comfortable."

### The 4 Budgets of Treating Chronic Pain

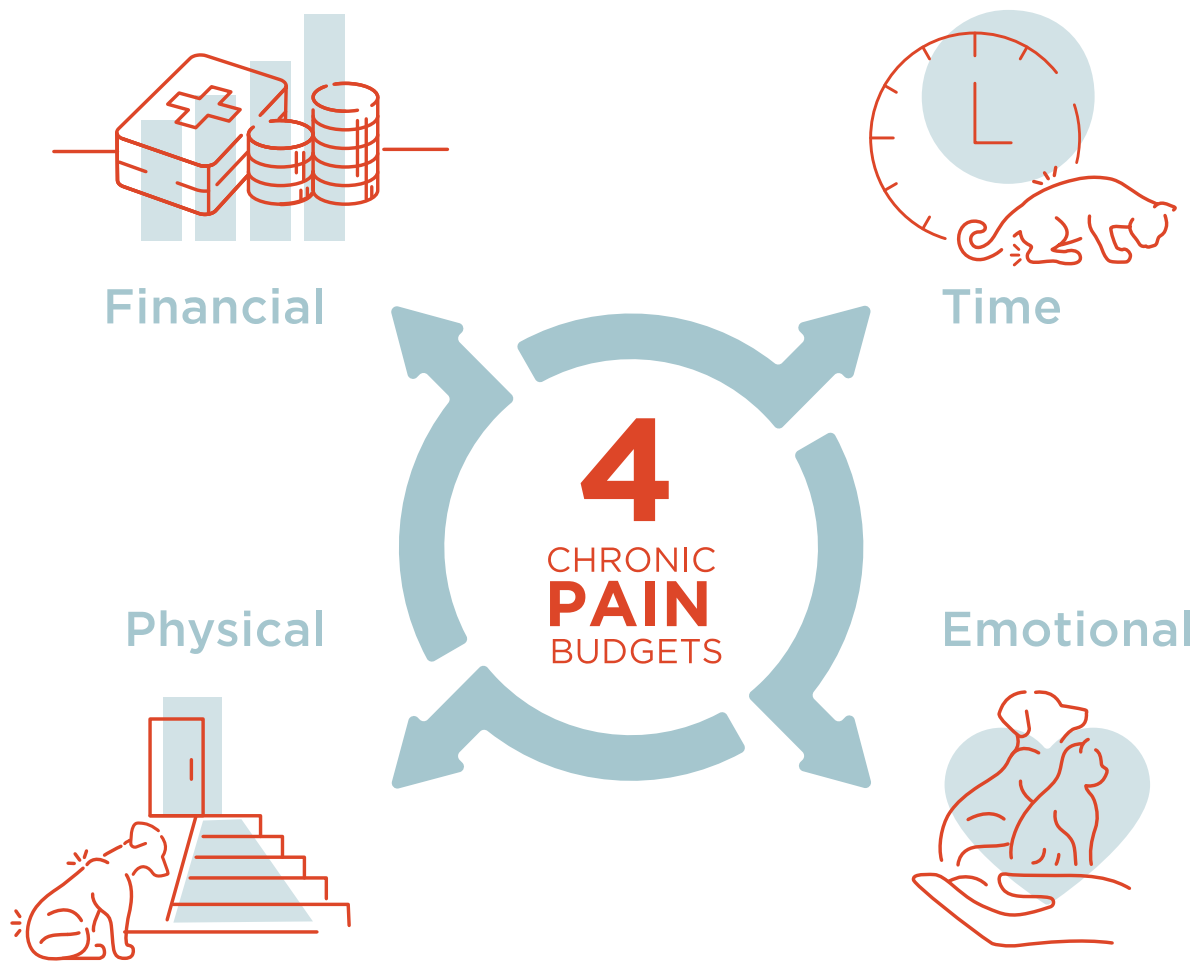
*"We always go over with owners that there are certain budgets that people have, and the word 'budget' immediately makes people think about how much money they have."*

–Dr. Robertson

When veterinarians talk about an owner's budget, everyone thinks, "Well, how much money does the person have to spend on his or her pet?" But Dr. Robertson points out that there are 4 "budgets" of treating chronic pain (**Figure 4**), all of which can contribute to lack of owner compliance and create gaps in therapy.

"Owners have 4 budgets, and if one of them is broken, then you're at a crossroads of where you're going. Everyone thinks a budget is just *money*, and it's not," explains Dr. Robertson. "There's the *emotional budget*, the successes, and sometimes the unsuccessful treatments. Owners need a *time commitment* for long-term care of a pet who has chronic disease. And then with very large dogs, we have to talk about the *physical budget*. If they are mobility impaired and they weigh 130 pounds and the owners are elderly, then we have a huge problem because they can't help their pet with his mobility if that's required. So we always look at the 4 budgets, and we want to keep all those budgets intact."

Figure 4. The four chronic pain budgets



Watch Dr. Gruen explaining how checklists can help identify osteoarthritis in cats:

[www.thenewscienceofopain.com](http://www.thenewscienceofopain.com)

**from the experts**



## CHAPTER III

# The Next Breakthrough in OA Pain Relief: An Innovative New Treatment



Watch Dr. Grubb and Dr. Budsberg explaining the impact of good treatment:

[www.thenewscienceofopain.com](http://www.thenewscienceofopain.com)

from the  
experts

The experts agree that pain relief is foundational to OA management, but we don't currently have a therapeutic option that provides consistent, profound pain relief. Therapy that targets NGF could lead to a long-lasting treatment for companion animals suffering with OA pain.

## Anti-NGF mAb Therapy

### What Is Anti-NGF mAb, and How Does It Work?

*"Most of us have a pretty firm understanding of how NSAIDs work. Anti-NGF mAb therapy will work the same way, but on a different receptor."*

– Dr. Grubb

"We know that NGF causes actual changes to the nerves themselves and how they function," says Dr. Steven Budsberg. "If we can prevent or mute that, that's very important. And if we can prevent those changes from occurring in other nerves and lessen the response in those that have been affected, then it's a benefit."

"What the monoclonal antibody [should] do is effectively block [the] activity [of NGF], sequester it from acting," he explains. "It's not going through the whole body and taking out all of the NGF. It's focused on the area of inflammation."



### Focus on Monoclonal Antibodies

There are nearly 100 monoclonal antibodies on the human side for various cancers that have truly revolutionized the treatment of cancer, Dr. Bergman explains. "You basically have to figure out what's your target of interest—whether that's cancer or pain or any other target. And then you go after that with a mAb," he says. "These agents are highly specific to your target of interest. We've seen that across a wide variety of different diseases, both in human medicine and on the veterinary side with Cytopoint®."

### The Role of Anti-NGF mAb Therapy in OA Pain

*"As we look at animals and pain, I say, 'This is how it is, but it's not how it should be.' And the anti-NGF mAbs will have that promise of giving these animals a life as they should have, not as they have to put up with."*

– Dr. Petty

“What’s the clinical relevance? Profound pain relief. A different mechanism than anti-inflammatory drugs,” Dr. Grubb concurs. “It’s only been NSAIDs so far. Now we have this other really powerful big player analgesic drug that could be available soon.”

“As an oncologist, I treat aged patients that often have a variety of comorbidities, including OA. When I think about the tools that we have in our toolkit presently, we have some that I would consider decent tools for dogs [with OA]. We have almost no good things in our toolkit on the feline side,” Dr. Philip J. Bergman says. “The promise of this remarkable agent is that I think it has a truly revolutionary chance to treat pain in our patients. We are all pet owners and pet lovers, and we know that these are things that our patients or our own personal pets are going to experience. The potential [for them] to have a remarkably improved quality of life is unbelievably exciting.”

### Anti-NGF mAb for Canine OA Pain Control

*“We will have a new way of controlling pain. And anti-NGF mAb therapy will have an advantage over traditional NSAID use because it’s an injectable and will always stay in your hands.”*

– Dr. Petty

Evidence tells us that dog owner compliance with NSAIDs is much lower than perceived by veterinarians. Because anti-NGF mAb will be administered in-clinic, anti-NGF mAb could potentially lead to:

- Less avoidance of use by pet owners
- Better pet owner compliance
- Continuous pain relief for pets
- Improved pain control over time

“There is going to be a specific subset of animals who are unable to tolerate NSAIDs,”

says Dr. Petty. “Those will be at the top of my list to contact when the anti-NGF mAbs come out.”

“With regards to the anti-NGF monoclonal antibody, it’s an agent that we know binds well to its target of interest in a very, very specific and species specific way,” Dr. Bergman says. “And instead of having to give a patient a pill daily or twice a day, this starts to become a game changer because you’re then giving it remarkably less frequently.”

### Anti-NGF mAb for Feline OA Pain Control

*“The promise of the anti-NGF mAb means that a lot of cats who are not getting treated for pain are going to get treated for pain. I think that when owners see what their cats are able to do — what their cats want to do —*

*when they’re free from pain, that can be a very powerful motivator to continue to give treatment.”*

– Dr. Gruen

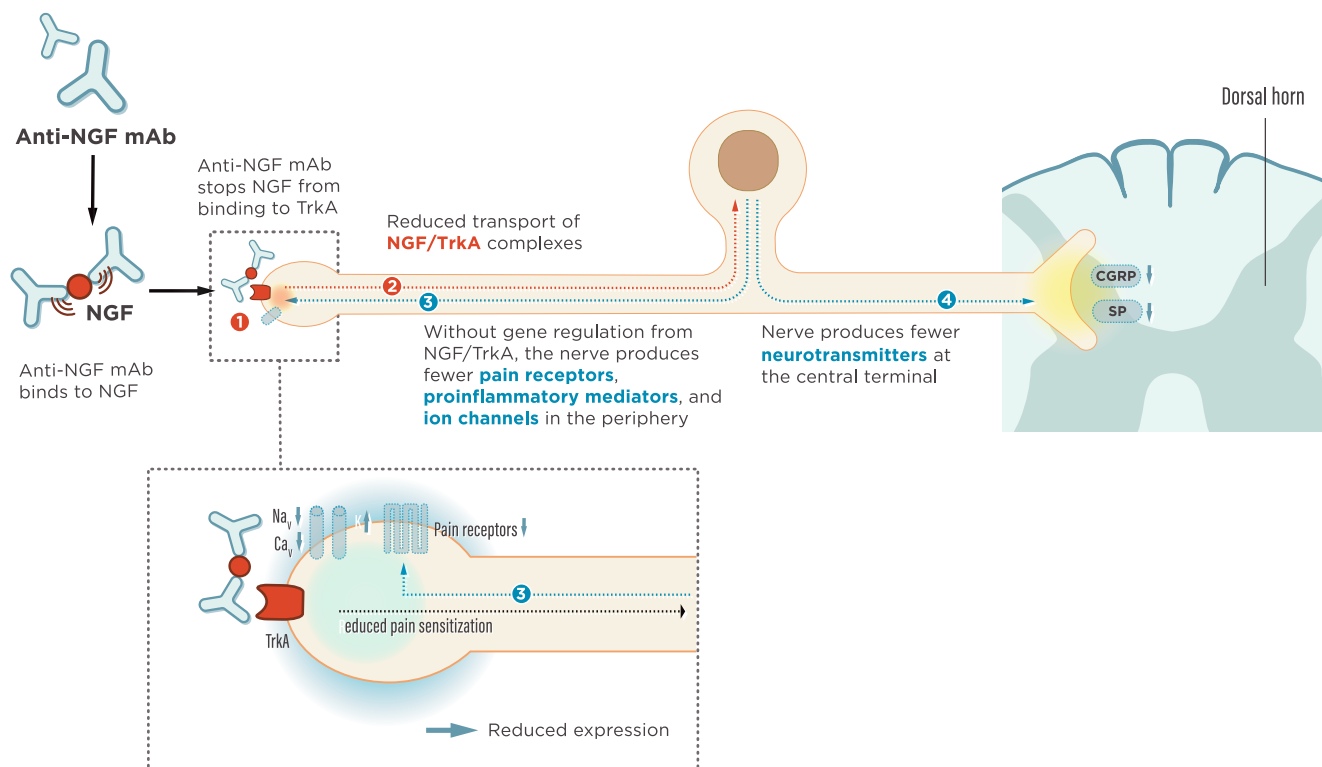
The sparse toolbox for addressing chronic feline pain does not meet the significant need (Figure 5).





## Figure 5. Anti-NGF mAb

Anti-NGF mAb is being studied as a biological, highly targeted treatment that would be given by injection once a month, to provide continuous relief. As a monoclonal antibody, it is broken down in the body into amino acids, like all other proteins. CGRP, calcitonin gene-related peptide; mAb, monoclonal antibody; NGF, nerve growth factor; SP, substance P; TrkA, tropomyosin receptor kinase A.



“Anti-NGF mAb will fill a huge hole in feline OA treatment. We have some things in our toolbox, but nothing like this,” Dr. Robertson says. “As everybody who has been owned by a cat knows, treating cats every day, especially with oral medications, is not an easy thing to do. It becomes aversive for the cat, and it’s very stressful for the owner. So with a single injection given, first of all, we can document the treatment has actually taken place. And the owners will be relieved knowing that they’re not going home with all these different pills and feeling like they’ve failed their pet if they can’t get him to take the medication.”

“For the cat owners, the anti-NGF mAb [should] be a real lifesaver,” says Dr. Petty. “Our options are very limited. We really need an

approved long-term chronic pain therapy, and the anti-NGF mAb [could] fit that bill.”

### Supporting the Human-Animal Bond: A Win for the Pet, Owner, and Veterinarian

*“The main goal is to enhance quality of life for the animal—so that means [managing] their pain [and giving them back] their ability to do what they like to do, to spend time doing the things that they want to do.”*

—Dr. Robertson




Enhancing quality of life for pets is the uppermost end-benefit of effective OA pain management because lasting pain relief helps pets to return to doing the things they want to do.

“I love being able to talk to clients confidently, and if I have a therapy I really believe in, I can honestly say to them, ‘I believe that you trust me because we have this relationship. I am your veterinarian, and you’re the caregiver, and we trust each other to do the very best we possibly can for this beloved cat,’” says Dr. Elizabeth Colleran. “I can say ‘I’ve seen the data. I know this works. I think we can make life better for you and for your cat.’”

“[The anti-NGF mAb could] be a very positive thing for owners, [knowing] that they have done the best for their pet,” Dr. Robertson says. “They haven’t failed them because they couldn’t get that pill in or those multiple pills in twice a day. And they have to be part of the team, because they’ll be doing other things to help their pet. But we’ve gotten over that huge

hurdle of the actual treatment that’s going to help their pet.”

“The development of the anti-NGF mAb will be really huge for pain management,” Dr. Grubb says. “The ability to alleviate this pet’s pain to me is quite obvious. The impact on the owner is also fairly obvious because the owner now is not frustrated. She’s able to help her pet, and that supports that human-animal bond. She can snuggle with her cat and go for walks with her dog, all the things they enjoyed. So win for the pet, win for the owner, and there is also a win for veterinary professionals, because that gives us another tool to support the promise that we made when we entered veterinary medicine, which says, in part, ‘I solemnly swear to use my scientific knowledge and skills for the protection of animal health and welfare and the prevention and relief of animals suffering.’ Pain is definitely a welfare and health issue, and animals in pain are suffering. This new drug [should] allow us this win, win, win situation.” 

# ZOETIS PETCARE

