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## The evolution of nerve growth factor inhibition in clinical medicine

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**Abstract** | Nerve growth factor (NGF) is a neurotrophin that activates nociceptive neurons to transmit pain signals from the peripheral to the central nervous system and that exerts its effects on neurons by signalling through tyrosine kinase receptors. Antibodies that inhibit the function of NGF and small molecule inhibitors of NGF receptors have been developed and tested in clinical studies to evaluate the efficacy of NGF inhibition as a form of analgesia in chronic pain states including osteoarthritis and chronic low back pain. Clinical studies in individuals with painful knee and hip osteoarthritis have revealed that NGF inhibitors substantially reduce joint pain and improve function compared with NSAIDs for a duration of up to 8 weeks. However, the higher tested doses of NGF inhibitors also increased the risk of rapidly progressive osteoarthritis in a small percentage of those treated. This Review recaps the biology of NGF and the studies that have been performed to evaluate the efficacy of NGF inhibition for chronic musculoskeletal pain states. The adverse events associated with NGF inhibition and the current state of knowledge about the mechanisms involved in rapidly progressive osteoarthritis are also discussed and future studies proposed to improve understanding of this rare but serious adverse event.

Chronic pain, especially from musculoskeletal conditions such as osteoarthritis (OA) and chronic low back pain (CLBP), affected more than 100 million individuals in the USA in 2008 and, in 2010, had an estimated annual cost of over US\$600 billion<sup>1</sup>. These estimates underscore the considerable public health burden of chronic pain and remind the medical community that diseases that cause pain are all too common. The currently available treatments for these ailments, such as paracetamol (acetaminophen), NSAIDs, opioids, tramadol and anti-depressant medications, can be effective but also have substantial limitations. In addition, the incidence of opioid-related hospitalizations among patients with musculoskeletal disorders has increased over the past two decades and continues to increase in individuals with OA<sup>2</sup>. Although important advances have sharpened our understanding of the pathophysiology of musculoskeletal pain, the majority of new pharmaceuticals have failed when translated from the laboratory to clinical trials.

Over the past two decades, nociceptive pain induced by neurotrophins via peripheral sensory nerve pathways has been carefully studied. This work led to the development of inhibitors of the neurotrophin nerve growth factor (NGF), which were initially studied in preclinical and clinical non-musculoskeletal conditions. NGF inhibitors, in the form of anti-NGF monoclonal antibodies that bind NGF and render it inactive, have also been evaluated for efficacy in the reduction of pain in

musculoskeletal and non-musculoskeletal disorders. Despite initial phase II and III clinical trials with NGF inhibitors demonstrating efficacy in reducing joint pain and improving function, reports of rapidly progressive OA (RPOA) of both the knee and hip joints emerged<sup>3</sup>. The incidence of RPOA resulted in the FDA halting the clinical trials for a period; a review of the clinical trials found that RPOA was associated with the higher doses of the anti-NGF antibodies used in the studies, and with the combined use of an anti-NGF antibody and an NSAID<sup>3</sup>. The clinical trial development programmes subsequently resumed using lower doses of the anti-NGF antibodies and, at the time of writing, a new drug application for the anti-NGF antibody tanezumab has been submitted to the FDA for review and approval.

In this Review, we cover the biology of NGF, the clinical studies performed to evaluate the efficacy of inhibiting NGF in chronic musculoskeletal pain states, the adverse events that subsequently developed and the investigations that have been performed to explain those adverse events. We also recommend future studies to improve the understanding of the rare but serious adverse event of RPOA.

### The biology of NGF

The discipline of neuroscience dates back to the late nineteenth century, when novel microscopy techniques became available that enabled the detailed study of the central nervous system (CNS). In work that resulted

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## Key points

- Chronic pain from osteoarthritis (OA) is highly prevalent, and effective non-opioid medications are few.
- Nerve growth factor (NGF) is an important neurotrophin that activates nociceptive neurons to transmit pain signals from the peripheral to the central nervous system.
- Treatment with anti-NGF antibodies inhibits joint pain and improves function in individuals with moderate to severe knee and hip OA.
- NGF inhibition is associated with rapidly progressive large joint OA; many theories exist as to why but the exact mechanisms involved remain unknown.
- Anti-NGF antibody treatments, if approved, should reduce pain and improve quality of life for individuals with knee and hip OA; however, safety monitoring programmes will be necessary.

in the 1906 Nobel Prize in Physiology or Medicine, Santiago Ramón y Cajal used silver nitrate staining techniques developed by Camillo Golgi to examine the CNS and found it to be composed of a network of depolarizing neurons interconnected with synapses<sup>4</sup>. This fundamental understanding paved the way for the development of the field. NGF was first described in 1951 and was initially found to control the growth and differentiation of embryonic sympathetic and sensory neurons<sup>5</sup>. Decades later, NGF was discovered to be present in adults and to have a role in tissue injury and pain<sup>6</sup>, which led to the study of NGF in health and various diseases. Important milestones in the history of NGF from the onset of neuroscience to the development of therapeutic antibodies are outlined in FIG. 1.

**NGF as a neurotrophin.** NGF belongs to a group of structurally related neurotrophins in the peripheral nervous system (PNS) and CNS. Important neurotrophins include NGF<sup>5</sup>, brain-derived neurotrophic factor (BDNF)<sup>7</sup>, neurotrophin 3 (NT3)<sup>8</sup>, NT4 (also known as NT5)<sup>9</sup>, NT6 (REF.<sup>10</sup>) and NT7 (REF.<sup>11</sup>). The nature and mechanism of action of neurotrophins is complex and thus not described here in detail (reviewed elsewhere<sup>12</sup>). Briefly, neurotrophins regulate neuron survival, growth and differentiation in the PNS and CNS during embryonic development. For example, BDNF mediates embryonic placode development of CNS sensory neurons. In addition, neurotrophins have an important role in the physiology of the nervous system in adulthood and are upregulated under pathological conditions.

Of all the neurotrophins, NGF has been studied in the greatest detail. The NGF molecule is composed of three subunits, called  $\alpha$ ,  $\beta$  and  $\gamma$ , and regulates the embryonic development of PNS sensory and sympathetic neurons from the neuronal crest: embryonic neuroblasts that lack NGF undergo apoptosis<sup>13</sup>. However, the presence of NGF is also required in adulthood; phenotypic knockout of NGF in adult mice (via the induction of anti-NGF antibodies) produces animals with skeletal muscle dystrophy and a reduced number of splenocytes<sup>14</sup>. Furthermore, these mice have smaller superior cervical ganglia and a reduced number of dorsal root ganglia (DRG) neurons compared with wild-type mice. Regarding the CNS in these mice, neurons that stained positive for anti-choline acetyl transferase were diminished in number and the learning capacity of the mice was impaired<sup>14</sup>. Thus, the presence of NGF seems to be obligatory for

both the PNS and the CNS, and perhaps also for the immune system of adult organisms.

**NGF signalling.** NGF binds to two separate receptors; p75 and tyrosine kinase A (TrkA)<sup>15</sup>. The low affinity receptor p75 is not necessary for NGF to achieve its biological function and might serve as a co-receptor<sup>16</sup>. By contrast, TrkA has a high affinity for NGF and belongs to a group of transmembrane receptors that have overlapping specificities for several other neurotrophins<sup>17,18</sup>. For example, TrkB selectively binds BDNF and NT4 (REF.<sup>19</sup>), and TrkC has a high affinity for NT3 (REF.<sup>20</sup>). When NGF binds to TrkA, the receptor complex is endocytosed and translocated to the nucleus of the DRG by retrograde axoplasmic transport. Within the DRG nucleus, phosphorylation of the NGF–TrkA complex induces gene transcription<sup>18,21,22</sup>. In adults, NGF induces the overexpression of other neuronal molecules, such as substance P<sup>23</sup> and calcitonin gene-related peptide (CGRP)<sup>24</sup>, in response to pain stimuli (including thermal, mechanical, electrical and UV irradiation) originating from nociceptors (FIG. 2a). These neurotransmitters are transported to spinal cord synapses for the transmission of action potentials to the CNS. However, they can also be released from the nociceptor itself after antidromal transport. In this situation, the neurotransmitters can then act as pro-inflammatory molecules to induce vasodilation and chemotaxis, causing subsequent local inflammation<sup>25</sup> (FIG. 2b). In addition, primary afferent nerve fibres have an increased excitability in response to NGF when acid-sensing ion channels<sup>26</sup>, transient receptor potential cation channel subfamily V member 1 (REF.<sup>27</sup>) and other receptors are activated. The result of this activation is an increase in the excitability of these fibres, termed peripheral sensitization. By contrast, changes to the CNS induced by ongoing pain stimuli lead to hyperexcitability and reduced neuronal inhibition, a phenomenon termed central sensitization<sup>28</sup>. In a clinical context, afferent nerve stimuli can cause an increased sensitivity to heat or touch stimuli, which can induce allodynia. Thus, stimulation of the nociceptor and internalization of the NGF–TrkA complex is converted to local inflammation and further pain sensation in a process called neurogenic inflammation (FIG. 2b).

In adult rats, 44% of low-calibre (<30  $\mu$ m) sciatic DRG neurons express TrkA, 27% express TrkB and 17% express TrkC<sup>29</sup>. The vast majority of visceral pelvic neurons express TrkA and TrkB, but express TrkC to a lesser extent. By contrast, afferent motor neurons express TrkB (50%) and TrkC (73%) but rarely TrkA (20%)<sup>29</sup>. These data suggest that TrkA and its ligand NGF are crucially important for pain perception in adult rats. However, TrkA is not only found on neurons but also exists on a variety of non-neuronal cells including human keratinocytes<sup>30</sup>, synovial fibroblasts<sup>31</sup>, mast cells<sup>32</sup> and all major types of peripheral leukocytes<sup>33</sup>. These data suggest that several distinct non-neuronal mechanisms are linked to NGF.

**NGF in joint tissues.** As a modulator of chronic pain, NGF represents a promising target for the treatment of pain associated with musculoskeletal diseases.

### Placode

Ectodermal structures in embryonic development that give rise to several different sensory systems.

### Dorsal root ganglia

The cell bodies of sensory nerves that transmit action potentials to the spinal cord.

### Retrograde axoplasmic transport

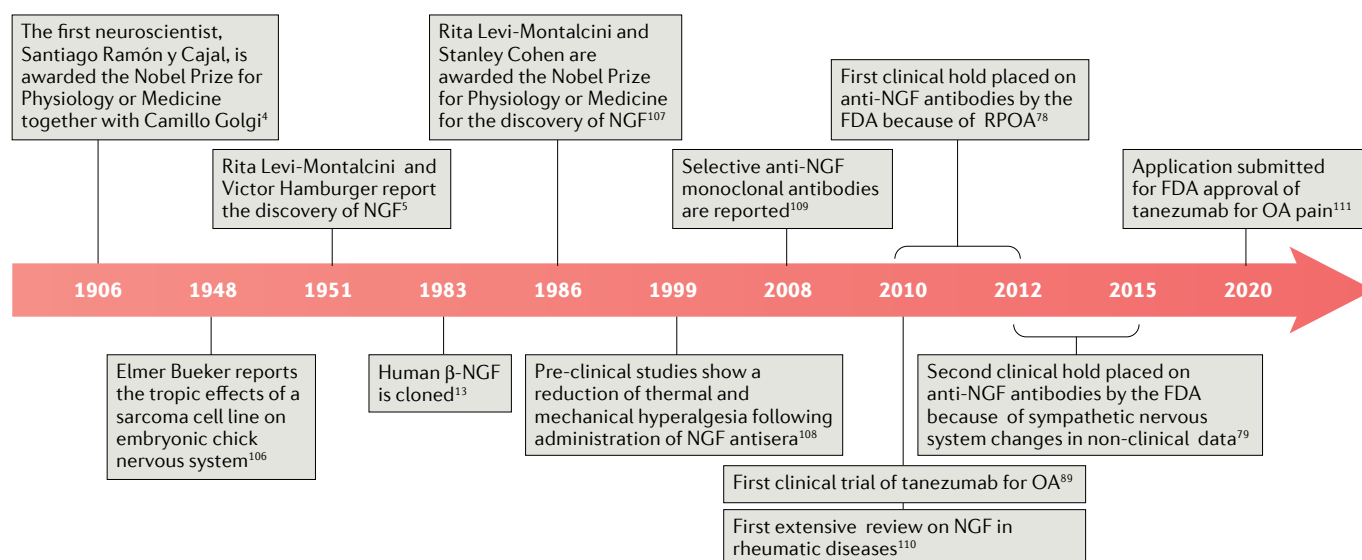
A process in which signalling molecules are moved from the periphery towards the cell body of an axon.

### Antidromal transport

Axoplasmic transport of signalling molecules from the nucleus to nociceptors.

### Allodynia

Painful sensation in response to non-painful stimuli.



**Fig. 1 | The evolution of NGF inhibition in clinical medicine.** A timeline showing some important steps in the development of nerve growth factor (NGF) inhibitors for use in clinical medicine, from the birth of neuroscience when Santiago Ramón y Cajal and Camillo Golgi were awarded the Nobel Prize for Physiology or Medicine in 1906, to the submission of tanezumab to the FDA for approval for use in the treatment of osteoarthritis (OA) in 2020 (REFS<sup>4,5,13,78,79,89,106–111</sup>). RPOA, rapidly progressive osteoarthritis.

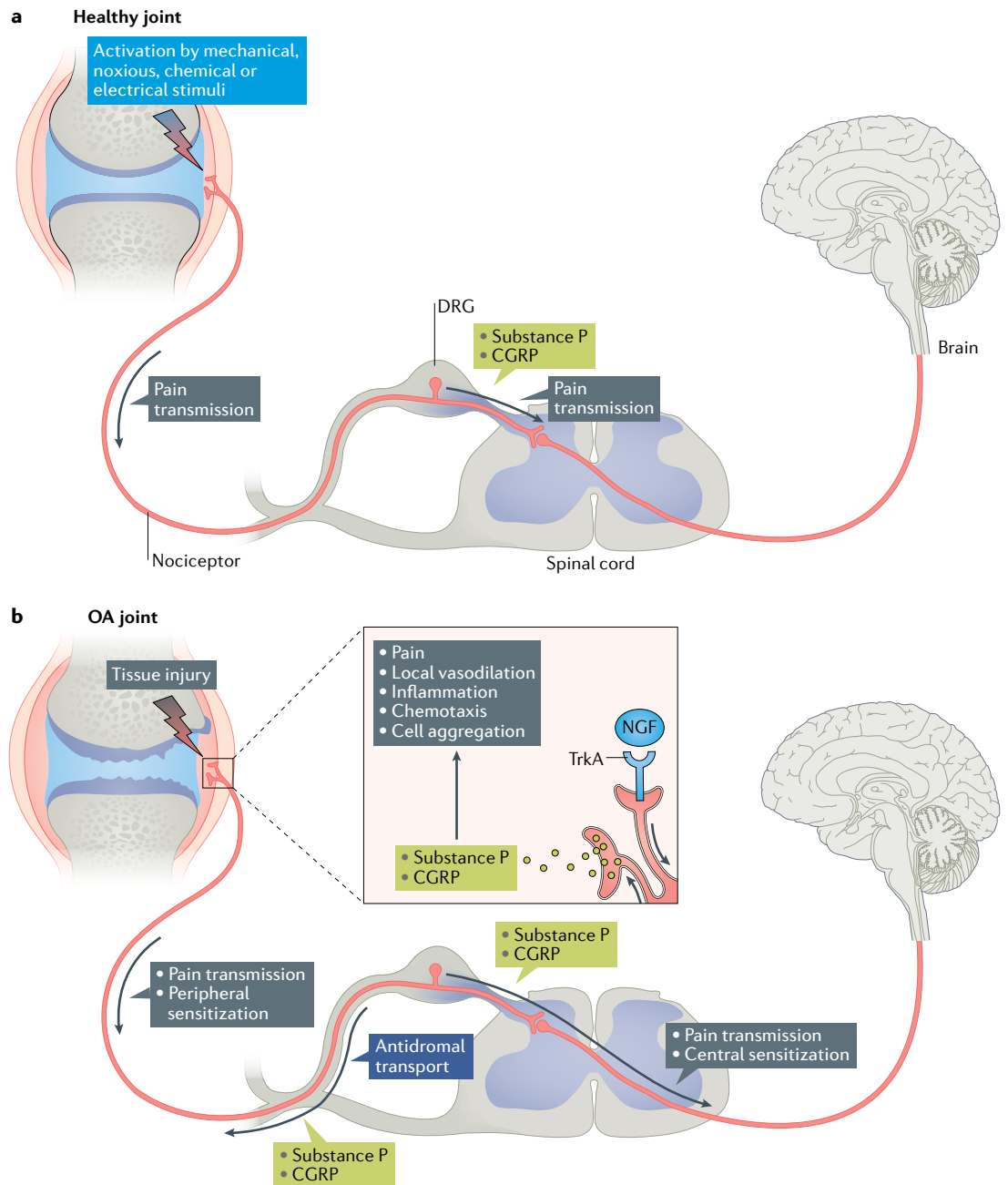
In addition, in the past decade, it has become clear that NGF is a pleiotropic molecule that affects the nervous system, bone and many other tissue compartments. Knowledge of NGF-mediated mechanisms beyond the nervous system is therefore crucial for understanding how systemic NGF inhibition might work and its potential adverse effects in patients with chronic pain. However, most of what is known about the effects of NGF on the musculoskeletal system comes from animal studies and contributes only indirectly to an understanding of the human musculoskeletal system.

NGF has an important role in bone metabolism and regeneration in animal studies. In healthy C57BL/6 mice, NGF is present in endothelial cells in the subchondral bone layer adjacent to the articular surface and scattered throughout the bone marrow<sup>34</sup>. Furthermore, TrkA and p75 expression is mostly limited to nerve fibres that are in close proximity to NGF-positive blood vessels. NGF also regulates sensory pain signals in the bone of rats in similar way to other parts of the periphery<sup>35</sup>; however, this signalling is a rapid, independent process that occurs before retrograde transport mechanisms and gene transcription can take effect. Experimental fracture or joint distraction models permit a detailed analysis of regenerative bone metabolism. In unfractured rat bone, osteoprogenitor cells express NGF<sup>36</sup>. After fracture, bone marrow stromal cells, osteoblasts and endothelial cells within newly formed capillaries are positive for NGF, and during subsequent callus formation, the periosteal matrix also gains positivity for NGF. In mice with tibial fractures, NGF also stimulates the formation of the callus by increasing the number of osteoblasts<sup>37</sup>. Topical application of  $\beta$ -NGF to cranial defects in rats induced the expression of  $\beta$ -III-tubulin and vascular endothelial growth factor, suggesting a regulatory role for neuronal growth and angiogenesis<sup>38</sup>. However, although

NGF inhibitor treatment did not inhibit callus formation in a closed femur fracture pain model in mice, it did reduce fracture-induced pain-related behaviour by ~50%<sup>39</sup>. These data suggest a regulatory and probably pro-osteogenic effect of NGF in murine models.

Preclinical models can also provide insight into potential favourable outcomes of clinical trials in humans<sup>40</sup>. For example, vaccination against NGF produced a substantial reduction in pain behaviour in mice with partial meniscectomy-induced OA<sup>41</sup>, providing further evidence that a decrease or depletion of NGF can be a powerful tool in reducing musculoskeletal pain. However, in human disease, the situation is similar in some ways and different in others. Results from experimental models of disease are sometimes difficult to interpret because they often involve an experimental procedure that does not exactly resemble human pathology. In addition, immune responses, connective tissue metabolism and pain perception mechanisms in animals can differ considerably from human physiology. The results from such animal studies thus resemble the human situation, but might not be identical. Therefore, the results from these studies should form the basis for experiments with human tissue.

OA has a pro-inflammatory cytokine profile similar to that found in rheumatoid arthritis (RA), but at a lower intensity. NGF, TNF and IL-6 are all present in knee synovial and meniscal tissue following injury<sup>42</sup>. In synovial fluid, NGF expression is present and higher in RA than in OA<sup>43</sup>. CD3<sup>+</sup> T cells and CD14<sup>+</sup> monocytes and macrophages from RA synovial fluid stain positive for NGF<sup>43</sup>, and NGF expression co-localizes with fibroblasts and some macrophages in synovium from patients with OA<sup>44</sup>. In vitro, substance P induces NGF overexpression both alone and in combination with IL-1 $\beta$  in OA synovial cells cultured in serum-free media<sup>45</sup>; a similar



**Fig. 2 | Principles of neurogenic inflammation in joint pain. a** | Occasional pain stimuli (mechanical, noxious, chemical or electrical) are transmitted from nociceptors in the joints to the nucleus of dorsal root ganglia (DRG) via action potentials, which trigger the transportation of neurotransmitters such as substance P and calcitonin gene-related peptide (CGRP) to the spinal cord. **b** | Chronic painful stimuli in the joints (such as those that occur in osteoarthritis (OA)) induce an increase in nerve growth factor (NGF), which binds to the high affinity receptor tyrosine kinase A (TrkA). The NGF–TrkA complex that is formed is translocated to the DRG nucleus and induces the overexpression of substance P and CGRP. These neurotransmitters convey pain signals to the spinal cord, but are also transported back towards the joints via antidromal transport and released at the nociceptor. In the joints, substance P and CGRP function as strong inducers of local inflammation. At the same time, NGF also induces increased excitability in the neuron by activating acid-sensing ion channels, resulting in peripheral hypersensitization. Chronic pain stimuli also change neuronal activity in the central nervous system by increasing membrane excitability or reducing axonal inhibition, known as central sensitization.

effect also occurs with TNF in combination with IL-1 $\beta$ <sup>31</sup>. In both RA and OA, osteochondral angiogenesis is accompanied by subchondral bone marrow replacement and NGF expression within vascular channels<sup>46</sup>. NGF is also expressed in subchondral mononuclear cells,

osteoclasts and chondrocytes in tissue from patients with knee OA<sup>47</sup>. In these individuals, NGF expression was associated with age and synovitis scores, suggesting an association with symptomatic OA and pain<sup>47</sup>. Preliminary data also suggest that NGF, TrkA and

**Zygapophyseal joints**  
Vertebral (facet) joints that  
interconnect the vertebral  
bodies.

other inflammatory mediators are present in human zygapophyseal joints, with NGF predominantly expressed in capsular synovial tissue and to some extent in the bone marrow, and TrkA mostly expressed in the bone marrow<sup>48</sup>. These studies demonstrate the presence of NGF in different target tissues and suggest that inhibitors of NGF might be a suitable and robust tool for reducing site-specific neurogenic inflammation and thus chronic pain.

**NGF in the CNS.** In rodents, NGF mediates the homeostasis of adult CNS neurons and is found in the hippocampus and cortex<sup>49</sup>. Treatment with NGF protects the CNS from degeneration in mice<sup>50</sup>. Conversely, anti-TrkA antibodies reduce the number and size of basal forebrain cholinergic neurons in rats<sup>51</sup>. This effect is transient, reversible and dependent on the stage of postnatal development. NGF might also have a role in Alzheimer disease, as there seems to be a degeneration of cholinergic neurons in the basal forebrain and hippocampus in mice with an experimental model of this disease<sup>52</sup>. Furthermore, the results of a 2018 clinical trial showed that intranasal administration of NGF could improve cognitive function in two patients with frontotemporal dementia<sup>53</sup>, suggesting a role for NGF in adult human CNS function. The results of these studies<sup>49–53</sup> imply that an intact blood–brain barrier is a prerequisite for the treatment of elderly individuals with NGF inhibitors. Therefore, any patient population with an impaired blood–brain barrier, such as after stroke and in those with multiple sclerosis, Alzheimer disease or neuroinflammatory disorders<sup>54</sup>, should be excluded from treatment with NGF inhibitors. Patients with chronic pain syndromes

such as OA are mostly advanced in age and thus develop considerable comorbidities that can include the cardiovascular system or the CNS. The latter is frequently characterized by neuronal degeneration and the loss of CNS function, such as Alzheimer disease. Therefore, these patients should be evaluated and carefully monitored before and during NGF inhibitor treatment.

### NGF inhibition in clinical trials

The importance of NGF in chronic pain has prompted the development of antagonists directed against NGF or neurotrophin receptors. A variety of small molecule inhibitors or antibodies have been investigated in both preclinical<sup>55–59</sup> and clinical studies<sup>60–63</sup> with varying degrees of success (TABLE 1). Larotrectinib, a small molecule inhibitor that targets TrkA, TrkB and TrkC, has been approved for the treatment of solid tumours<sup>64</sup>, whereas another small molecule inhibitor, ASP7962, which is an oral selective TrkA antagonist, did not show efficacy in a phase IIa trial in patients with knee OA<sup>63</sup>. Although several monoclonal antibodies have been studied extensively in human OA and other chronic pain conditions, the clinical development of most molecules has been discontinued for a variety of reasons. Only tanezumab and fasinumab are currently under clinical investigation for OA and CLBP and are discussed in the following sections. The relationship of these agents with RPOA and joint destruction and replacement is complicated and is addressed in a later section.

**Hip and knee osteoarthritis.** Monoclonal antibodies that bind to NGF have been tested for efficacy in reducing pain in both knee and hip OA in phase II and

Table 1 | Inhibitors of NGF and NGF receptors

Name	Chemical properties	Specificity	Investigations	Refs
ALE-0540	Non-peptidic molecule	TrkA and p75	Studied in allodynia in rats	55
TrkAd5	Soluble receptor protein	TrkA	Studied in an experimental OA model in mice	56
MNAC13	Recombinant mouse anti-TrkA antibody Fab fragment	TrkA	Studied in basal forebrain cholinergic neurons in rats	94
K252a	Small molecule inhibitor	TrkA	Studied in experimental psoriasis using a SCID mouse–human skin transplantation model	58
ABT-110 (PG110)	Humanized mAb	NGF	Studied in hypersensitivity in rats; clinical trials discontinued	59,95
Larotrectinib (ARRY-470)	Small molecule inhibitor	TrkA, TrkB and TrkC	FDA approved for malignant solid tumours	64
ASP7962	Small molecule inhibitor	TrkA	Phase II RCT in knee OA	63
Tanezumab	Humanized mAb	NGF	Clinical trials in hip and knee OA, chronic low back pain, acute bunionectomy, chronic prostatitis/chronic pelvic pain syndrome, interstitial cystitis, neuropathic pain and pain from bone metastases	96
Fasinumab	Fully human mAb	NGF	Clinical trials in OA, acute sciatic pain and chronic low back pain	97
Fulranumab	Fully human mAb	NGF	Clinical trials in post-herpetic neuralgia, post-traumatic neuropathy, cancer-related pain, hip and knee OA, interstitial cystitis, chronic low back pain and diabetic peripheral neuropathy; investigations discontinued	98

mAb, monoclonal antibody; NGF, nerve growth factor; OA, osteoarthritis; RCT, randomized controlled trial; SCID, severe combined immunodeficiency; Trk, tyrosine kinase receptor.



phase III clinical trials. In this section, we review trial reports and meta-analyses of the anti-NGF antibodies tanezumab, fulranumab and fasinumab that have been published since our previous review of the topic in 2013 (REF.<sup>65</sup>). The salient points from the studies are summarized in TABLE 2, and the study details are listed fully in Supplementary Table 1.

NGF inhibition has been studied in knee and hip OA both together and separately. The primary end points that have been almost universally utilized in these studies are the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain and function subscales, which are combined with physician's global assessment (PGA) scales in many studies. The WOMAC is a well-validated measure that is widely used by the OA research community; thus, the use of it in the majority of these studies allows for comparison and facilitates meta-analysis of the data. In general, these studies show that anti-NGF antibodies produce a significant improvement in pain, function and PGA scores compared with placebo for both knee and hip OA (Supplementary Table 1). However, anti-NGF antibodies carry an increased risk of adverse events compared with placebo that are primarily of a peripheral neurological nature. Meta-analyses performed on data from the anti-NGF antibody clinical trials have shown that these agents have a significant but modest effect and are superior to placebo for the main study end points, but are variable in terms of superiority compared with active NSAID treatment. These meta-analyses also reaffirmed the safety findings of the individual studies: anti-NGF antibodies increased peripheral neuropathy and sensation adverse events, but there were no significant differences in serious adverse events compared with either placebo or NSAID treatments. Overall, the number of clinical trials and the relative consistency of their findings with regard to pain and function outcomes, along with multiple meta-analyses that have reported similar findings, provide relatively robust support for the efficacy of anti-NGF antibodies for the treatment of painful knee or hip OA. By contrast, a single phase IIa trial of a TrkA inhibitor reported no effect of the agent when compared with placebo and inferiority to naproxen for WOMAC pain scores<sup>63</sup>; given the paucity of data related to the use of TrkA inhibitors for the treatment of pain in OA, it is probably too early to draw definite conclusions.

The number of studies that have been performed using NGF inhibitors enables some interesting observations to be made. One point of interest is the time course of efficacy for pain inhibition in knee and hip OA using these agents, which was reported in some but not all of the studies in TABLE 2. In many of the tanezumab studies, it seems that clinical efficacy (as measured by the WOMAC pain score) begins at week 4 after initiation of treatment<sup>66–70</sup> and persists through to either week 16 (REFS<sup>67,69,70</sup>) or week 24 (REFS<sup>66,68</sup>). Of the two studies in which fulranumab was investigated for the treatment of knee or hip OA, one provided no information about outcomes at multiple time points<sup>71</sup> and the other was difficult to interpret owing to the large number of study groups<sup>72</sup>. The authors of the single study of fasinumab for

this indication reported significant pain improvement that was superior to placebo starting at week 2 (least squares mean change from baseline  $-0.7$  in the placebo group and  $-1.4$  to  $-1.6$  in the fasinumab groups) and persisting through to week 16 (REF.<sup>73</sup>) (Supplementary Table 1). The fact that pain relief is consistently reported to begin at around 2–4 weeks in these studies might be informative for a discussion of expectations with patients, if one or more of the agents are eventually approved and used in clinical practice.

When considering the efficacy of anti-NGF antibodies for the indications of knee and hip OA, it is important to consider whether the medications improve function in addition to whether they improve pain. In many of the clinical trials, function was a co-primary end point along with pain outcomes, most commonly measured using the WOMAC function score. Notably, in each study in which the anti-NGF antibody demonstrated superiority to the comparator (placebo or an NSAIDs) for pain measures, there was also superiority over the comparator for functional improvement.

Interestingly, the most recent phase III study of tanezumab for knee or hip OA (published in 2020) found that the higher dose of subcutaneously administered tanezumab (5 mg) was associated with improvements in all three co-primary endpoints (WOMAC pain score, WOMAC function score and PGA), but the lower dose (2.5 mg) was not associated with an improvement in PGA<sup>74</sup>. A previous study of subcutaneously administered tanezumab (using doses of 2.5, 5 and 10 mg) that was published in 2018 was terminated owing to an FDA hold on clinical trials and was therefore underpowered compared with the intended recruitment goal<sup>67</sup>. Studies prior to these<sup>67,74</sup> used an intravenous formulation of tanezumab and demonstrated efficacy in all end points at lower doses (2.5 mg or 5 mg) as well as doses up to 10 mg (TABLE 2). The results of the 2020 phase III subcutaneous tanezumab study suggests that the lowest doses of subcutaneous tanezumab might be at the lower limits for achieving a valuable clinical reduction in pain and improvement in quality of life<sup>74</sup>.

**Chronic low back pain.** Two clinical trials and one meta-analysis have been published since 2013 on the use of NGF inhibition (specifically tanezumab) for CLBP, another painful musculoskeletal condition (Supplementary Table 1). Overall, an effect for NGF inhibition was detected for this indication, but was only small to moderate in magnitude and was, in some studies, only present for the higher doses of the agent. Whether this result represents a different degree of efficacy for tanezumab than that observed for hip or knee OA is currently unclear.

The results of a phase IIb study in which three doses of tanezumab (5, 10 or 20 mg every 8 weeks) were compared with either naproxen (500 mg twice daily) or placebo were reported in 2013 (REF.<sup>75</sup>). In the study, the change in daily average low back pain intensity was evaluated between baseline and week 16. The two higher doses of tanezumab (10 mg and 20 mg) were superior to both naproxen and placebo, but the lowest dose of tanezumab (5 mg) was only superior to placebo.

Table 2 | Trials and meta-analyses of anti-NGF antibody therapy for osteoarthritis

Study	Target joint (number of participants)	Agent (comparator)	Study conclusions	Adverse events	Ref
<b>Clinical trials</b>					
Brown et al. (2012)	Knee (690)	IV tanezumab 2.5 mg, 5 mg or 10 mg (placebo)	Tanezumab was superior to placebo for all end points	More common in tanezumab groups than placebo groups, mostly paraesthesia and hypoaesthesia; RPOA not reported	68
Birbara et al. (2018)	Knee or hip (379) <sup>a</sup>	SC tanezumab 2.5 mg, 5 mg or 10 mg (IV tanezumab 10 mg or placebo)	All tanezumab groups had greater improvement than the placebo group at all time points; final analyses not performed owing to FDA clinical hold	Marginally more TJRs in tanezumab groups (n = 3) than in placebo groups (n = 2); only 1 TJR with imaging was reviewed, which was judged to show normal progression of OA	67
Birbara et al. (2018)	Knee or hip (678) <sup>a</sup>	SC tanezumab 2.5 mg, 5 mg or 10 mg (not controlled)	All tanezumab doses resulted in improvements in all outcomes	34 TJRs; majority in tanezumab 10-mg group; of the adjudicated TJRs, half were judged to be normal OA and half RPOA	67
Schnitzer et al. (2015)	Knee or hip (2,700)	IV tanezumab 5 mg or 10 mg with or without an NSAID (placebo with an NSAID)	Pain and function improved more in all tanezumab groups than in the placebo with NSAID group; tanezumab with NSAID was superior to placebo with NSAID for PGA; tanezumab monotherapy was equivalent to tanezumab with NSAID for pain and function	Higher in all tanezumab groups than in the placebo with NSAID group; highest in the tanezumab with NSAID group (specifically paraesthesia and hypoaesthesia); worsening OA and osteonecrosis more common in tanezumab with NSAID groups; TJRs twice as common in tanezumab with NSAID group than in tanezumab monotherapy or placebo with NSAID groups; RPOA reported in 34 participants, more common in tanezumab groups than in the placebo with NSAID group	99
Spierings et al. (2013)	Hip or knee (610)	IV tanezumab 5 mg or 10 mg (placebo or oxycodone)	Both tanezumab doses had more improvement in pain than either the placebo or the oxycodone group	Highest rate in the oxycodone group; 2 TJRs (hip) in the higher dose tanezumab group; 1 TJR was judged to be normal OA and the other RPOA	100
Balanescu et al. (2014)	Knee or hip (604)	IV tanezumab 2.5 mg, 5 mg or 10 mg with diclofenac (placebo with diclofenac)	All tanezumab groups were superior to placebo with diclofenac for all co-primary outcomes	TJR more common in all tanezumab groups (1.3–2.1%) than in the placebo with diclofenac group (0.7%); serious adverse events were similar in tanezumab groups (5.3–7.6%) and in the placebo with diclofenac group (5.3%); adjudication confirmed one case of RPOA, but some cases did not have sufficient radiographs for a judgement to be made	66
Ekman et al. (2014)	Knee (828)	IV tanezumab 5 mg or 10 mg (placebo or naproxen)	Tanezumab at both doses was superior to placebo for all co-primary endpoints; tanezumab 5 mg but not 10 mg was superior to naproxen for pain and PGA; both tanezumab doses were superior to naproxen for function	Serious adverse events were not more common in the tanezumab groups (2.9–3.4%) than in the placebo (3.8%) or naproxen (2.4%) group; 3 TJRs reported, only one of which was in the tanezumab 5-mg group; 2 TJRs were judged to be worsening OA, but there was insufficient information to make a decision about RPOA	69
	Knee or hip (840)	IV tanezumab 5 mg or 10 mg (placebo or naproxen)		Serious adverse events were not more common in the tanezumab groups (1.4–1.9%) than in the placebo (1.9%) or naproxen (4.3%) groups; 3 TJRs reported, none of which was in the tanezumab groups; 1 TJR was judged to be worsening OA, but unclear whether it could have been RPOA	
Schnitzer et al. (2019)	Knee or hip <sup>b</sup> (698)	IV tanezumab 2.5 mg or 2.5 mg then 5 mg (placebo)	Both tanezumab groups had a greater reduction in all co-primary end points than the placebo group	Similar across all groups, except that abnormal peripheral sensation adverse events were more common in the tanezumab groups than in the placebo group; TJRs more common in both tanezumab groups than in the placebo group and showed a dose–response pattern; RPOA noted in the tanezumab 2.5-mg group (2.2%) and in the tanezumab 2.5-mg then 5-mg group (0.4%); no RPOA in the placebo group	83
Schnitzer et al. (2020)	Knee or hip <sup>b</sup> (696)	IV tanezumab 2.5 mg or 2.5 mg then 5 mg (placebo)	Both tanezumab groups had a greater reduction in all co-primary end points than placebo at week 2 and at week 16		101
Berenbaum et al. (2020)	Hip or knee (849)	SC tanezumab 2.5 mg or 5 mg (placebo)	The tanezumab 5-mg group had a greater reduction in all end points than the placebo group; the tanezumab 2.5-mg group was only superior to the placebo group for WOMAC outcomes	Both tanezumab groups had more hypoaesthesia than the placebo group; the tanezumab 5-mg group had more paraesthesia than the placebo group; RPOA in 1.4% of the tanezumab 2.5-mg group, 2.8% of the tanezumab 5-mg group and none in the placebo group; TJRs were similar across all groups (6.7–7.8%)	74



Table 2 (Cont.) | Trials and meta-analyses of anti-NGF antibody therapy for osteoarthritis

Study	Target joint (number of participants)	Agent (comparator)	Study conclusions	Adverse events	Ref
<b>Clinical trials (cont.)</b>					
Mayorga et al. (2016)	Knee (196 randomized and 65 completed 12 weeks) <sup>c</sup>	Fulranumab 3 mg or 9 mg (placebo or oxycodone)	Both fulranumab groups had superior outcomes to the oxycodone group but not to the placebo group	Neurological adverse events were higher in the fulranumab groups than in the placebo group, but similar to the oxycodone group; 4 TJRs, 3 in the fulranumab groups and 1 in the oxycodone group; no TJRs were judged to be RPOA	71
Sanga et al. (2017)	Knee or hip (401)	Fulranumab 1 mg or 3 mg every 4 weeks or 6 mg or 10 mg every 8 weeks (placebo)	Long-term improvement in the two fulranumab 4-week groups and in the fulranumab 10-mg 8-week group compared with the placebo group for all outcomes	Neurological adverse events were more common in the fulranumab groups than in the placebo group; 81 TJRs in 71 individuals, including 25 in non-index joints; 21% of TJRs were judged to be RPOA, all of which were in participants receiving fulranumab and also taking NSAIDs	72
Dakin et al. (2019)	Knee or hip (342)	Fasinumab 1 mg, 3 mg, 6 mg or 9 mg (placebo)	All fasinumab groups had greater improvements at all end points than the placebo group	More common in the fasinumab groups than in the placebo group; 25 arthropathies noted, primarily in the fasinumab groups and showing a dose-related pattern; 18 TJRs occurred that were evenly distributed across all groups; 16 cases of RPOA were detected, all in fasinumab groups	73
<b>Systematic reviews and meta-analyses</b>					
Schnitzer and Marks (2015)	Knee or hip (8,606)	Tanezumab, fulranumab and fasinumab (placebo)	Tanezumab at all doses was superior to placebo for all end points with no difference in effect size across the doses; fulranumab and fasinumab seemed superior to placebo overall	Withdrawals owing to adverse events for tanezumab were generally similar to placebo; fulranumab and fasinumab were not different from placebo for withdrawal owing to adverse events as there were too few adverse events for analysis; for all anti-NGF antibody groups combined, there was borderline statistical significance for increased withdrawal owing to adverse events compared with placebo; RPOA was not discussed	102
Kan et al. (2016)	Knee (1,839)	Tanezumab (placebo)	Tanezumab was superior to placebo for all outcomes	Serious adverse events were similar for tanezumab and placebo; tanezumab was associated with increased peripheral neuropathy and withdrawal owing to adverse events compared with placebo; RPOA was not discussed	103
Chen et al. (2017)	Knee and hip (7,665)	Tanezumab (placebo or placebo with an NSAID)	Tanezumab was superior to placebo or placebo with an NSAID for all outcomes	Serious adverse events were similar for tanezumab and placebo or placebo with an NSAID; tanezumab was associated with increased paraesthesia and hypoaesthesia and withdrawal owing to adverse events than placebo or placebo with an NSAID; RPOA was not discussed	104
Tive et al. (2019)	Knee or hip (7,491)	IV tanezumab 2.5 mg, 5 mg or 10 mg with or without an NSAID (placebo or placebo with an NSAID)	Tanezumab was superior to placebo for all end points; only the two higher doses of tanezumab were superior to placebo with an NSAID for all outcomes	Tanezumab was associated with an increased incidence of abnormal peripheral sensation adverse events; overall incidence of adverse events was stated to be similar across groups but no statistical analysis was reported; RPOA not evaluated for the different groups in the studies	105

IV, intravenous; NGF, nerve growth factor; OA, osteoarthritis; PGA, physician's global assessment; RPOA, rapidly progressive osteoarthritis; SC, subcutaneous; TJR, total joint replacement; WOMAC, Western Ontario and McMaster Universities Arthritis Index. <sup>a</sup>Trial was underpowered owing to FDA clinical hold. <sup>b</sup>Excluded radiographic 'joint safety conditions' (RPOA, fracture or osteonecrosis). <sup>c</sup>Trial halted early owing to FDA clinical hold.

Adverse events were more common in participants who received tanezumab than in those who received placebo or naproxen; in particular, arthralgias, headaches and paraesthesia were noted in those who received tanezumab. Interestingly, there were no total joint replacements (TJRs) for any reason in this study, despite the relatively large samples size ( $n = 1,347$ ).

An uncontrolled randomized trial has also been performed to evaluate the long-term safety and efficacy of tanezumab for CLBP<sup>76</sup>. 848 participants were drawn from a parent study for inclusion in the trial and received 10 mg or 20 mg tanezumab every 8 weeks as

three rounds of intravenous administration followed by four rounds of subcutaneous administration. Outcomes were the change from parent study baseline in Brief Pain Inventory Short Form, Roland Morris Disability Questionnaire and PGA for low back pain. Both tanezumab doses were associated with persistent and similar efficacy for all the defined outcomes. The most common adverse events were arthralgia, paraesthesia and hypoaesthesia, which occurred at frequencies similar to those in other studies. Thirteen patients had TJRs, and adjudication of eight of those TJRs revealed one instance of RPOA.

## Paraesthesia

Abnormal skin sensation without stimulation.

## Hypoaesthesia

Numbness of the skin with a reduction of sensations to sensory stimuli.

Finally, a single meta-analysis of the use of anti-NGF antibodies for the treatment of CLBP has been published<sup>77</sup>. The authors identified only randomized controlled trials that met their criteria, two using tanezumab, one using fasinumab and one using fulranumab. The quality of the evidence generated by this meta-analysis was low or very low for pain relief, functional improvement and adverse effects using the Grading of Recommendations Assessment, Development and Evaluation criteria, indicating that the reader should be cautious when interpreting the available findings. Overall, the authors of this meta-analysis reported a small effect for pain (0.29 standard deviations below placebo) and for functional improvement (0.21 standard deviations below placebo) and an increased number of adverse events compared with placebo at 12–16 weeks (relative risk (RR) 1.13; 95% CI 0.98–1.29), primarily for neurological adverse events (RR 1.93; 95% CI 1.41–2.64)<sup>77</sup>. The difference in magnitude of effect size of anti-NGF antibodies between CLBP and knee OA could potentially relate to the fact that CLBP includes multiple disease entities, including facet joint OA, discogenic pain and muscle-related pain, and the efficacy of anti-NGF antibodies for these various entities could differ considerably.

#### Adverse effects of anti-NGF antibodies

During the phase II and III clinical trials of the tanezumab development programme, unexpected adverse events (including osteonecrosis and rapid destruction of joints) were reported by the study site investigators, such that the FDA placed a partial clinical hold on studies of tanezumab for all indications other than cancer pain between 2010 and 2012 (REF.<sup>78</sup>). This clinical hold was eventually extended to cover all anti-NGF monoclonal antibodies that were in clinical development.

Another partial clinical hold was instituted by the FDA on all anti-NGF antibody programmes from 2012 to 2015 after a report of reductions in the size and number of neurons in the sympathetic nervous system of adult mice<sup>79</sup>. Investigations were subsequently instituted to determine the aetiology and potential clinical relevance of these findings, including a series of studies in which cynomolgus monkeys were treated with tanezumab<sup>80</sup> and a systematic review of clinical records from participants in tanezumab clinical trials, which was presented at the American Academy of Neurology conference in 2015 (REF.<sup>81</sup>). The investigations found no evidence of sympathetic nervous system dysfunction and the FDA allowed the clinical studies of tanezumab to resume with sympathetic function disorder as a new exclusion criterion.

**Independent adjudication of anti-NGF antibodies.** To try to understand the risks associated with the use of anti-NGF antibodies, adjudication was performed by independent committees of experts. The adjudication committee formed for the studies of tanezumab undertaken by Pfizer reviewed all of the information for cases of adverse events and developed validated definitions for assessments of the radiographs that included osteonecrosis, worsening OA, another condition or

insufficient information to determine if the case was OA or osteonecrosis<sup>3</sup>. Overall, 386 study participants experienced an adverse event and underwent TJR in the tanezumab phase III studies in OA ( $n=373$ ) and in the phase II study in CLBP ( $n=13$ ). In the OA studies, the TJRs were in the index joint in 216 participants and in a non-index joint in 170 participants; however, 74.7% of those who received TJR in a non-index joint had evidence of OA in the affected joint and the remaining ~25% had either insufficient information (20%), another joint abnormality (3.5%) or a normal joint or minimal OA (1.8%)<sup>3</sup>. Of the 13 participants who underwent TJR in the phase II CLBP study, OA was present in the affected joint in 11 participants and there was insufficient information for 2 participants. In total, adverse events were adjudicated in 249 participants from the tanezumab studies: 47.8% ( $n=119$ ) of the events were labelled as normal OA progression, 27.3% ( $n=68$ ) as RPOA and 0.8% ( $n=2$ ) as osteonecrosis<sup>3</sup>. The committee determined that there was no association between TJR and the dose of tanezumab monotherapy; the overall TJR rate for tanezumab monotherapy was similar to that of the comparators, and both of those rates were similar to the placebo and not statistically significant<sup>3</sup>. However, when tanezumab was administered in combination with an NSAID, the rate of TJRs increased in line with increasing doses of tanezumab and was about two to three times the rate of TJR in those receiving placebo. The time to a TJR was not associated with the dose of tanezumab used; however, the time to TJR decreased when tanezumab was combined with an NSAID, especially with the 5-mg or 10-mg doses of tanezumab<sup>3</sup>.

The adjudication committee also reviewed those participants who developed RPOA ( $n=68$ ; hip (56%), knee (40%) and shoulder (4%))<sup>3</sup>. RPOA was subclassified as either type 1 or type 2, with type 1 indicating a  $\geq 1$ -mm loss of joint space width in less than 1 year and type 2 indicating bone loss or destruction at a level not normally associated with end-stage OA, including catastrophic bone failure and joint destruction. RPOA of both types occurred in 67 participants from the OA studies and in 1 participant from the CLBP study. 43 instances of RPOA (63%) occurred in the index joints and 25 (37%) in non-index joints; of the non-index joints, 15 (60%) had definitive OA at a pre-study visit, 9 (36%) had unknown status of the joint at a pre-study visit and 1 (4%) had another abnormality<sup>3</sup>. The participants who developed RPOA were more likely to be women and to have increased joint pain after the baseline study visit. Importantly, the incidence of RPOA was associated with the dose of tanezumab monotherapy used; 2.5 mg tanezumab was associated with 0 events per 1,000 patient years, whereas 10 mg tanezumab was associated with 11 events per 1,000 patient years<sup>3</sup>. The incidence of RPOA in participants who received tanezumab with an NSAID was significantly increased compared with the comparator, with hazard ratios ranging from 8.76 (95% CI 1.05–73.40) for 2.5 mg tanezumab with an NSAID to 17.50 (95% CI 2.37–129.40) for 10 mg tanezumab with an NSAID<sup>3</sup>. These data clearly demonstrate a dose–response relationship between

tanezumab and RPOA and an added contribution from NSAIDs.

In addition to tanezumab, adjudication of TJRs was also performed for phase II studies of fulranumab for OA. In these studies, 108 joints were replaced, of which 64% were from normal progression of OA, 18% from RPOA, 14% had insufficient information to make a diagnosis, 4% were revision TJRs and none had osteonecrosis<sup>72</sup>. Safety results have also been reported for a phase IIb/III study of fasinumab in OA ( $n=342$ )<sup>73</sup>. Adjudicated arthropathies were detected in 25 joints (13 index joints and 12 non-index joints) from 23 participants, totalling 7% of those who received fasinumab and 1% of those who received placebo. The joint-related adverse events were dose dependent. 14 patients developed type 1 RPOA and 2 patients developed type 2 RPOA following fasinumab treatment, whereas no patients developed RPOA with placebo treatment. In addition, subchondral insufficiency fractures occurred in 1.8% of patients who received fasinumab at any dose and in 1.2% of those who received placebo. On the basis of these data<sup>73</sup>, the sponsor of these studies modified their clinical development plan to only include doses of 1 mg fasinumab every 4 weeks and 1 mg fasinumab every 8 weeks in an ongoing phase III study, the results of which should be available within the next year.

**Tanezumab follow-up studies.** Once the FDA hold was released, tanezumab studies recommenced in individuals with painful knee or hip OA, but at reduced doses (2.5 mg and 5 mg). The preliminary results of one study that included 2,996 patients with OA have been reported, in which tanezumab was administered by subcutaneous injection every 8 weeks and compared with oral NSAID use for 56 weeks with 24 weeks of follow-up<sup>82</sup>. During the 80 weeks in which the participants were monitored, the time-adjusted rate of events per 1,000 patient years for the primary composite joint safety end point was higher for those receiving 2.5 mg tanezumab (37.4 events per 1,000 patient years) and 5 mg tanezumab (71.5 events per 1,000 patient years) than for those receiving NSAIDs (14 events per 1,000 patient years). Rates of type 1 and 2 RPOA were higher in those receiving tanezumab treatment than in those receiving NSAIDs, as were the rates of TJRs, which ranged from 25.7 events per 1,000 patient years with NSAID treatment to 51.8–79.7 events per 1,000 patient years with tanezumab treatment. These results show that even when using lower doses, the risks of joint deterioration remain greater with tanezumab treatment than with NSAID treatment<sup>82</sup>.

In another phase III study, subcutaneous tanezumab (two doses of 2.5 mg (2.5-mg tanezumab group) or one dose of 2.5 mg followed by one dose of 5 mg (2.5/5-mg tanezumab group)) was compared with placebo for pain reduction in individuals with knee or hip OA ( $n=582$ )<sup>83</sup>. No adjudicated joint safety events occurred between weeks 0 and 16; however, over the 40-week treatment and post-treatment follow-up period, a total of 25 joint safety adverse events occurred in participants receiving tanezumab and 5 in participants receiving placebo. RPOA was diagnosed in 5 individuals in the 2.5-mg tanezumab group, in 1 individual in the 2.5/5-mg tanezumab group

and in no-one receiving placebo. Abnormal peripheral sensation adverse events were reported up until the end of the study, including paraesthesia (11 in those receiving tanezumab versus 1 in those receiving placebo) and hypoesthesia (11 in those receiving tanezumab versus 6 in those receiving placebo)<sup>83</sup>. Other clinical trials of subcutaneous tanezumab at 2.5-mg and 5-mg doses for OA have not yet been published<sup>84,85</sup>; thus, a more complete picture of the efficacy and adverse event profile for this treatment is still pending.

The mechanisms that underlie the RPOA associated with tanezumab treatment, either alone or in combination with NSAIDs, are currently unclear. Possible explanations include neuropathic neuropathy, in which the loss of ability to feel pain leads to abnormal joint loading, and analgesic neuropathy, in which reduced joint pain could lead to overloading of the joint and rapid deterioration. The latter explanation had been previously proposed for a similar situation involving indomethacin, following the results of a study in which individuals waiting for hip replacements were randomly allocated to receive azapropazone or indomethacin<sup>86</sup>; after ~2 years of follow-up, participants who received indomethacin had more radiographic joint destruction and joint pain than those who received azapropazone. However, given that the risk of TJR increased when tanezumab was used in conjunction with an NSAID, mechanisms related to changes in inflammation, pain reduction and reduced prostaglandin E2 production within the joint have been proposed. Another possible cause might be related to changes in the mass and architecture of the subchondral bone, as individuals with knee and hip OA who have atrophic radiographic changes have accelerated joint destruction and more joint replacements than those who have a greater amount of juxta-articular bone mass<sup>87</sup>.

Additional studies have been performed in an attempt to refine the phenotype of those who will go on to receive TJR, determine the effects of NSAIDs and discover potential bone, cartilage, soft-tissue or inflammatory biomarkers that were associated with TJR. A post hoc analysis of data from clinical trials of tanezumab in OA that included 47 participants who developed RPOA and 92 who did not aimed to discover biomarkers by comparing those who used NSAIDs for <90 days with those who used NSAIDs for ≥90 days over a 10-month period<sup>88</sup>. Two serum biomarkers, C3M (a marker of synovial tissue inflammation) and C2M (a marker of cartilage degradation) predicted type 2 RPOA in those who used NSAIDs for <90 days with an accuracy of 71%, and individuals with this biomarker phenotype had an 8-fold higher risk of developing RPOA than patients with OA without this phenotype<sup>88</sup>. These results are intriguing; however, additional validation is needed before these biomarkers can be recommended for identifying individuals at high risk of RPOA.

### Unanswered questions concerning RPOA

The adverse events of RPOA and peripheral sensation changes were not anticipated in either the preclinical studies or phase I clinical studies of anti-NGF antibody therapies. Although many hypotheses exist around how RPOA occurs, to date there is no clear understanding

of the risk profile of patients with OA who are likely to develop RPOA. The changes in peripheral sensation might be linked to the underlying mechanism of NGF inhibition reducing nociceptor activity; however, more work is needed to refine this idea. Neurological sensory adverse events are generally reversible upon discontinuation of the medication, although some individuals reported that analgesia was still present at the termination of the studies<sup>89</sup>. By contrast, RPOA is not reversible. Preclinical studies that determine the fate of nociceptors during anti-NGF antibody treatment and clinical studies that refine the phenotype of patients with OA who might be at risk of RPOA will help clinicians to identify those patients who would benefit the most from these novel analgesic therapies.

The few preclinical studies that have specifically evaluated the effects of NGF inhibition on both pain behaviour and joint structure were described in a 2017 review<sup>90</sup>. These studies evaluated the effects of treatment with soluble NGF receptors, small molecule inhibitors of TrkA or anti-NGF antibodies. The studies that only assessed pain demonstrated a reduction in pain using reduced weight-bearing asymmetry as an end point<sup>90</sup>. Studies that assessed both pain and histological or radiographic joint changes reported reduced gait imbalances following NGF inhibitor treatment compared with controls that were maintained up to 35 days, and an increased knee diameter in NGF inhibitor-treated animals that differed from control-treated animals<sup>90</sup>. A study that used a model of rat medial meniscal injury in which treatment with a humanized anti-NGF antibody (tanezumab) was initiated at the time of the injury and continued for 28 days reported that tanezumab-treated animals were protected against gait deficiency; however, rats treated with tanezumab at any dose had increased cartilage damage, subchondral bone sclerosis and tibial osteophytes compared with those treated with control substances<sup>91</sup>. In another study in rats with monosodium iodoacetate-induced OA, treatment with an anti-NGF antibody at the time of injury prevented weight-bearing asymmetry, but there was increased cartilage damage in the treated knee at day 28 compared with vehicle controls<sup>92</sup>. When anti-NGF antibody treatment was delayed to either 14 or 21 days after injury, the treated rats had a decrease in weight-bearing asymmetry and mechanical allodynia at day 28, and although there was no clear difference in the amount of cartilage damage, there was a decrease in osteoclast numbers at the tibial plateau in anti-NGF antibody-treated rats compared with saline-treated rats<sup>92</sup>. Overall, these studies confirm the considerable analgesia observed in the clinical trials of anti-NGF antibodies and that these therapies are effective at treating different stages of OA. However, these studies also provide evidence of cartilage degeneration, synovitis and osteoclast activity in the subchondral bone that is different in NGF inhibitor-treated animals than in control-treated animals. The joint damage reported in the animal studies was greater when the NGF inhibitor treatment was initiated in the early stages of the disease<sup>91,92</sup>.

Although NGF inhibitors are effective at reducing pain in animal models of OA and in patients with OA,

a gap still exists in our knowledge of how the joint can rapidly degenerate so, on this point, we are speculating about the mechanisms. NGF signals through the TrkA and p75 receptors on nociceptors, thereby promoting the expression of ion channels and neuropeptides in neurons that contribute to the innervation of the joint microenvironment. Thus, inhibition of NGF signalling and subsequent deficits in neuronal signalling and innervation could potentially alter the microenvironment within the joint, which might then result in accelerated joint degeneration. Given that nerves and blood vessels grow in congruence with each other and nociceptors regulate blood flow, a relatively rapid reversal from enhanced NGF signalling in OA to a near complete loss of NGF signalling could potentially also cause a dramatic change in synovial innervation and blood flow, thereby compromising the joint. In addition, as bone is loaded, osteocytes within the bone signal to the bone surface to direct remodelling of the tissue to accommodate the loads. Bone remodelling is associated with NGF; thus, inhibition of NGF signalling could also potentially interfere with normal loading signals, further altering the structural integrity of the joint<sup>46</sup>. In fact, mice that lack TrkA have reduced bone formation under loading conditions compared with wild-type mice, suggesting that this receptor is required for load-induced bone formation<sup>93</sup>. Clearly, more research into the interaction between the nerves, vasculature and the rest of the joint microenvironment is needed to explore this issue.

## Conclusions

Over the past 70 years, our understanding of the biology of the neurotrophin NGF has expanded from a factor that stimulates the growth of embryonic sensory and sympathetic neurons to a factor with an important role in arthritis and in modulating the PNS. Early-phase and late-phase clinical trials have determined that NGF inhibition with subcutaneous tanezumab or fasinumab is an effective form of analgesia for knee and hip OA and for CLBP. The analgesic efficacy of these anti-NGF antibodies is noteworthy because of their completely novel mechanism of action that lacks the adverse effects associated with conventional NSAIDs, opioids and steroids, and their demonstrated efficacy in patients with painful large joint OA. However, adverse events including RPOA and insufficiency fractures of the tibia have been reported that have to be carefully considered. Although the aetiology of these events is not yet fully understood, it is reasonable to expect that if these medications are approved for the treatment of pain associated with knee and hip OA, clinicians will need to inform their patients about these risks. Moving forwards, it will be crucial to identify patient characteristics that increase the risk of RPOA during anti-NGF antibody treatment. If we are able to identify risk factors for RPOA, the use of anti-NGF antibodies in clinical practice for large joint OA and other treatment-resistant chronic pain syndromes would be safer and more appealing.

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# Author contributions

M.F.S. and N.E.L. researched data for the article. All authors contributed substantially to discussions of content, wrote the article and reviewed or edited the manuscript before submission.

# Competing interests

B.L.W. declares that he received a research grant from Pfizer from 2011 to 2012. M.F.S. declares that he has been a consultant for Eli Lilly and Pfizer, and that he has received educational grants from these companies. N.E.L. declares that she has performed phase II and phase III clinical trials for Pfizer (2010–2012 and 2016–2019) and has been a consultant for Pfizer (2011–2019).

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# Review criteria

A search focused on the biology of nerve growth factor was performed in Medline, Medpilot, the Information Centre for Life Sciences in Cologne, Germany and libraries in Basel and Bern, Switzerland. The search terms used were “nerve growth factor”, “pain”, “neurogenic inflammation”, “neurotrophin”, “substance P”, “brain-derived neurotrophic factor”, “calcitonin gene-related peptide”, “osteoarthritis”, “collagen-induced arthritis”, “low back pain”, “therapy” and “cytokines” alone and in combination. A further search for clinical studies published between 2012 and 2020 was performed in PubMed and Embase. The search terms used were “knee or hip osteoarthritis”, “nerve growth factor”, “NGF”, “tropomyosin kinase receptor” and the names of individual agents alone or in combination. Relevant reports of trials and meta-analyses were included and conference abstracts, animal studies, publications in languages other than English and articles discussed in our 2013 review<sup>45</sup> were excluded. We also searched the reference lists of the identified articles for further relevant papers.

# Supplementary information

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